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ERRATA.

Vol., 1939, **36.**

Page Line

337   22   for " *Ester* " read " *Ether.*"

337   24⎫
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ANNUAL REPORTS

PROGRESS OF CHEMISTRY.

RADIOACTIVITY AND SUBATOMIC PHENOMENA.

INTRODUCTORY AND SUMMARY.

THE year 1940 has produced no spectacular progress in nuclear physics. The "boom" in papers about nuclear fission—the break-up into two roughly equal fragments of the nuclei of the heaviest elements—which followed the discovery of this remarkable phenomenon early in 1939 has almost faded out. On the other hand, investigation of the radioactive isotopes produced by the bombardment of various elements with neutrons and with artificially accelerated projectiles such as protons, deuterons, and α-particles is being pursued in many places and with ever more powerful methods. Long-lived isotopes of common elements such as hydrogen, carbon, chlorine, and calcium were discovered and are likely to gain great importance as tracers in chemical and biological investigations. Radioactive isotopes of the elements 85 and 93 have been produced and have made possible the study of the chemical properties of these elements. The phenomenon of nuclear isomerism—the occurrence of nuclei with identical charge and mass but different radioactive properties—has been extensively studied and a number of cases have been elucidated, thanks largely to the use of the β-ray spectrograph. No less than four cases of nuclear isomerism have been found among the isotopes of indium alone, and about 24 pairs of nuclear isomers can now be regarded as well established, there being some evidence for another 10.

The accurate determination of the magnetic moment of free neutrons is perhaps the most important item in the field of neutron research. The scattering of slow neutrons by crystals was studied by several investigators. They found, in agreement with theory, that diffraction effects play a considerable part and cause the scattering from a large crystal to be much less than from the same amount of a fine powder where diffraction is negligible. Since some of the older measurements of nuclear cross-sections were

done with crystals as scatterers, their results are likely to need revision.

NUCLEAR FISSION AND TRANSURANIC ELEMENTS.

The work of this year has brought only confirmation and some slight extensions of the knowledge gained in 1939, which was fully reported upon last year.

The number of ions produced by the fission fragments of uranium and thorium was again the subject of several investigations.[1] Kanner and Barschall confirm the earlier result that the distribution curve shows two maxima corresponding to mean kinetic energies of 64 and 97 m.v.   In addition, they proved that a particle of one group is always associated with a particle of the other group.   They used a thin layer of uranium, sputtered upon a very thin aluminium foil which enabled both fragments to escape into the ionisation chamber so that their total ionisation was measured.   In this arrangement, only one maximum was observed, corresponding to an energy of 151 m.v., which agrees well with the sum of the two energies given above, allowance being made for an energy loss of about 8 m.v. in the aluminium foil.   Jentschke and Prankl [1] find that the minimum between the two maxima is less pronounced if fission is produced by fast rather than slow neutrons.   This must mean that with increasing neutron energy more symmetrical fission modes become possible, a result which is confirmed by chemical evidence (see below).

Cloud-chamber photographs of the tracks produced by fission fragments [2] show numerous " branches " on each track, resulting from close collisions between the fragments and nuclei of the gas. N. Bohr [3] showed that, on account of the large mass and charge of the fission fragments, nuclear collisions are much more important for them than for α-particles or protons, which lose their energy almost exclusively by collisions with electrons.   The energy loss of fission fragments was also studied by Haxel [1] (experimentally) and by W. E. Lamb [4] (theoretically).

Chemical analysis of the fission products of uranium and thorium, which led to the identification of more than 30 radioactive periods in 1939, has been continued.   Only a few new periods, however, were discovered, and nearly all the results summarised in last year's table still hold good.

[1] W. Jentschke and F. Prankl, *Physikal. Z.*, 1939, **40**, 706; O. Haxel, *Z. Physik*, 1939, **112**, 681; M. H. Kanner and H. H. Barschall, *Physical Rev.*, 1940, **57**, 372.
[2] K. J. Brostrøm, J. K. Bøggild, and T. Lauritsen, *Physical Rev.*, 1940, **58**, 651.
[3] *Ibid.*, p. 654.   [4] *Ibid.*, p. 696.

G. N. Glasoe and J. Steigman [5] used the method, described last year, of bubbling air through a uranium salt solution during or after irradiation with neutrons, the air bubbles carrying with them all the isotopes of krypton and xenon which result from the fission. By placing a negatively charged wire in the air sample, the decay products of these gases were collected and subsequently subjected to chemical separations. By comparing the initial activities resulting from successive extractions from the same gas sample, the half-life of the respective parent gas could be determined.

Apart from [88]Rb, of 18 mins. period, the growth of which from a 3-hours krypton was confirmed, the authors found that a rubidium isotope of 15·4 mins. grows from a krypton isotope with a period of a few minutes and decays into an isotope of strontium with a half-life of about 51 days. This long-lived strontium has been known for some time and is probably [89]Sr.

In addition, the authors confirmed the growth of a 33-mins. cæsium from a 17-mins. xenon, but found no evidence of its decay into a long-lived barium (see last year's *Report*). According to their evidence, the 300-hours barium grows from a very short-lived cæsium isotope, which is formed from an equally short-lived xenon.

Two longer-lived xenon isotopes were studied in two different places [6] with substantially identical results. A genetic relation was established between two known activities : the 5·5-days xenon was found to grow from the 22-hours iodine, and a new xenon activity, with a period of 9·4 hours, was found to grow from a 6·6-hours iodine. Both these xenon periods result also from thorium fission, but with different relative intensity. Segrè and Wu [6] also showed that an isotope of element 43, decaying with a half-life of 6·6 hours, can be extracted from the 67-hours molybdenum which results from uranium fission, thus confirming the identification of the latter as [99]Mo or [101]Mo.

A zirconium isotope of 17-hours period, decaying into a 75-mins. columbium, and some evidence for a zirconium with more than 20-days period, was found by A. V. Grosse and E. T. Booth.[7] This fills the gap in the light group of fission products, so that now active isotopes of all the elements between bromine and element 43 and between antimony and lanthanum have been found among the products of the fission of uranium with slow neutrons.

The gap between the two groups seems to be real as far as fission

[5] *Physical Rev.*, 1940, **58**, 1.

[6] E. Segrè and C. S. Wu, *ibid.*, **57**, 552; R. W. Dodson and R. D. Fowler, *ibid.*, p. 966.

[7] *Ibid.*, p. 664.

by slow neutrons is concerned.   Active isotopes of silver, cadmium, and indium have, however, been produced [8] by irradiation of uranium with very fast neutrons, produced by deuteron bombardment of lithium.   The two silver periods found, of 7·5 days and 3 hours, agree with the known periods of ^{111}Ag and ^{112}Ag.   Of the three cadmium periods, of 50 mins., 5·5 hours, and 2·5 days, the last two decay into active indium isotopes of 2·1 hours and 4·5 hours, respectively, which is strong evidence for their identity with ^{117}Cd and ^{115}Cd.   All these activities are not produced by thermal neutrons, or even by the neutrons from beryllium, bombarded with deuterons.

It seems likely that an increase in the energy of the bombarding neutrons would extend the range of the mass ratio of the fission fragments, not only towards smaller values, as indicated by these experiments (and those of Jentschke and Prankl, see above), but also towards larger values; *i.e.*, elements below bromine and above lanthanum would be produced.   It seems, however, that at present not even all the active substances produced in slow-neutron fission are known.   E. Fermi [9] estimates that the added activities of all the known fission products account for only about one-half of the total, chemically unseparated, activity of irradiated uranium (after allowance for the presence of active isotopes of uranium and element 93, see below), and suggests that the surplus may be due in part to unknown active isotopes of rare-earth elements.

Fission of uranium under deuteron bombardment, briefly reported last year, was further studied by R. S. Krishnan and T. E. Banks,[10] who also obtained positive results with thorium.   Photo-fission, *i.e.*, fission caused by γ-rays (from fluorine, bombarded with protons), was observed by R. O. Haxby, W. E. Shoupp, W. E. Stephens, and W. H. Wells,[11] both for uranium and for thorium.   The weakness of the effect explains why earlier observers had failed to detect it. Evidence for spontaneous fission of uranium (but not of thorium) was reported by Flerov and Petrjak.[12]   From the brief note (cabled) it is not clear to what extent the effect—which would correspond to a mean life of 10^{16} to 10^{17} years—was caused by the neutrons known to accompany the cosmic radiation.

It was mentioned in last year's *Report* that N. Bohr,[18] from an analysis of the energy dependence of the fission phenomena, had concluded that the fission observed with neutrons of thermal energy

[8] Y. Nishina, T. Yasaki, H. Ezoe, K. Kimura, and M. Ikawa, *Nature*, 1940, **146,** 24.
[9] *Ibid.,* p. 640.   [10] *Ibid.,* **145,** 860.
[11] *Physical Rev.,* 1940, **58,** 92.   [12] *Ibid.,* p. 89.
[18] *Ibid.,* 1939, **55,** 418; N. Bohr and J. A. Wheeler, *ibid.,* **56,** 426.

was to be ascribed to the light isotope of uranium, ^{235}U, which constitutes 0·7% of ordinary uranium. This conclusion has now been confirmed by experiments with separated isotopes.[14] Samples containing a few micrograms of the heavy isotope, and correspondingly smaller samples of the light one, were prepared by means of a mass spectrograph. When these samples were subjected to an intense bombardment with slow neutrons, fission was observed in the light but not in the heavy isotope. It was also found that the rare isotope ^{234}U (U-II) does not contribute appreciably to the fission effects in ordinary uranium.

With regard to the emission of neutrons in uranium fission, new measurements [15] and a careful analysis [16] of earlier experiments indicate that the average number of neutrons emitted per fission is close to 3. This figure is somewhat larger than the estimate (2·3) given in last year's *Report*, but the situation concerning the possibility of a nuclear chain reaction has not been materially changed thereby.

Instead of causing fission, a neutron hitting a uranium nucleus may be captured. It has been known for some time that the irradiation of uranium with slow neutrons produces a β-active isotope of uranium, with a period of 24 mins., and there was strong evidence that this was ^{239}U rather than ^{236}U. This, too, has now been confirmed by experiments with separated isotopes.[17] In addition, the growth of an active substance of 2·3-days period from ^{239}U has been observed [18] and had to be ascribed to the formation of an active isotope of element 93. Preliminary experiments on the chemical behaviour of this new element showed that it is precipitated quantitatively by hydrofluoric acid in the presence of a reducing agent (sulphur dioxide), cerium being used as a carrier. In the presence of an oxidising agent (bromate in strong acid) it is not precipitated. In the reduced state with a thorium carrier it is precipitated by iodate, and in the oxidised state with uranium as sodium uranyl acetate. It is also precipitated with thorium on the addition of hydrogen peroxide, and in basic solution if carbonate is excluded. These properties indicate that its two valency states are similar to those of uranium, the chief difference being in the value of the oxidation potential between the two valencies, such that the lower state is more stable in the new element. It has

[14] A. O. Nier, E. T. Booth, J. R. Dunning, and A. V. Grosse, *Physical Rev.*, 1940, **57**, 546, 748; K. H. Kingdon, H. C. Pollock, E. T. Booth, and J. R. Dunning, *ibid.*, p. 749.

[15] T. Hagiwara, *Mem. Coll. Sci., Kyoto Imp. Univ.*, 1940, *A*, **23**, 19.

[16] L. A. Turner, *Physical Rev.*, 1940, **57**, 334.

[17] E. T. Booth, J. R. Dunning, A. V. Grosse, and A. O. Nier, *ibid.*, **58**, 475.

[18] E. McMillan and P. H. Abelson, *ibid.*, **57**, 1185.

little if any resemblance to its lower homologue, rhenium, for it is not precipitated by hydrogen sulphide in acid solution, is not reduced to the metal by zinc in acid solution, and does not have an oxide volatile at red heat.

Since $^{239}93$ emits (negative) β-rays, it must form $^{239}94$. The latter probably decays into ^{235}U by the emission of an α-particle. No α-particles were, however, observed from a strong, aged sample of $^{239}93$, and it is concluded that the life of $^{239}94$ must exceed 10^6 years. Moreover, no fission fragments were observed, so spontaneous fission is improbable, too.

If uranium is bombarded with very fast neutrons (from lithium + deuterons) a β-active uranium isotope with a half-life of 7 days is produced.[19] Since slow neutrons fail to produce this activity it is attributed to ^{237}U, resulting from ^{238}U by a $(n, 2n)$ (neutron-loss) reaction. In decaying it must form $^{237}93$, but no activity due to this isotope was discovered when element 93 was extracted (see above) from an aged sample of ^{237}U.

ARTIFICIAL RADIOACTIVITY.

The study of artificial radioactivity has made great strides during the last few years, and a comprehensive report by G. T. Seaborg,[20] which covers the literature up to July 15th, 1940, lists more than 350 different periods, of which more than 150 can be attributed to definite isotopes. This progress is due in part to the ever-increasing number of workers in this field, but mainly to the development of experimental resources. In the first place, the construction of numerous cyclotrons and their development towards greater beam intensity and higher energy must be mentioned. The most powerful instrument at present is the 60-inch cyclotron at Berkeley, which produces deuterons up to 16 m.v. and helium nuclei (α-particles) up to 32 m.v. energy. Particles of these energies can readily penetrate even into the heaviest nuclei. The strong activities which thereby become available greatly facilitate the chemical identification of the various periods and permit us to unravel genetic relationships by means of successive chemical separations which necessitate the measurement of small fractions of the initial activity. Increasing use is being made of the β-ray spectrograph to study both the continuous energy spectrum of the β-rays (positive or negative electrons) emitted from the nucleus itself and the superimposed " lines " of electrons of sharply defined energy, which have been

[19] Y. Nishina, T. Yasaki, H. Ezoe, K. Kimura, and M. Ikawa, *Physical Rev.*, 1940, **57**, 1182; E. McMillan, *ibid.*, **58**, 178.

[20] *Chem. Reviews*, 1940, **27**, 199.

ejected from the K- or L-shell of the atom by the internal conversion of nuclear energy.   Although two different radioactive substances may have the same half-life within the limits of experimental error, it is very unlikely that the energy spectra of the particles which they emit should be identical as well, and the β-ray spectrograph is thus of great help in the identification (or otherwise) of activities of similar half-life.

The spacing and intensity of the electron lines give information about excited states of the nucleus concerned, and have been particularly useful in the study of isomeric nuclei (see below).   In some β-ray spectrographs the photographic plate has been replaced by a counting tube, which in this way records single electrons within a narrow range of energies.   This arrangement is more sensitive and more suitable for quantitative intensity measurements than the photographic plate.   By setting it for any one electron line, the decay of the substance emitting this line can be determined with little disturbance from the presence of other activities.

Long-lived Isotopes of Common Elements.—The discovery of ^{3}H, a β-active isotope of hydrogen, was briefly announced in last year's *Report.*   Evidence for a decay with a few months' half-life was reported but soon withdrawn again ; the apparent decay had been due to diffusion through a rubber tube.   An indirect determination of the period gave a value of about 30 years.[21]   A known number of ^{3}H nuclei was produced by exposing lithium for a certain time to a known density of slow neutrons [reaction ^{6}Li (n, α) ^{3}H] and the number of nuclei decaying per second was determined by dissolving the lithium in water and introducing a known fraction of the hydrogen evolved into a tube counter.   From these data, it is possible to calculate the time after which all the nuclei would have decayed if decay continued at its initial rate.   By multiplying this time (the mean life) by 0·69, one obtains the half-life.   The β-rays of ^{3}H are exceedingly soft, their maximum energy being only 0·013 m.v. ;   it is therefore necessary to introduce any material containing ^{3}H into the counter, in gaseous form, in order to observe the activity.

Another interesting isotope is ^{14}C, the radioactivity of which was first observed by S. Ruben and M. D. Kamen.[22]   It had been known for some time that ^{14}C is produced in various nuclear reactions such as ^{14}N(n, p), ^{13}C(d, p), and ^{11}B(α, p), and from the energy balance in these reactions a β-radiation of about 0·3 m.v. energy was expected. Ruben and Kamen found that the β-rays of ^{14}C are much softer,

[21] R. D. O'Neal and M. Goldhaber, *Physical Rev.*, 1940, **58**, 574.
[22] *Ibid.*, **57**, 549.

only about 0·1 m.v., which explains the earlier failures to detect this activity. No decay has been observed, but from an estimate of the number of nuclei produced by the reaction $^{13}C(d, p)^{14}C$, and the number decaying per time unit, the period must be at least 1000 years. ^{14}C should become very useful as a tracer in chemical and biological work, where its long period will permit the study of slow processes, for which the period (20 mins.) of ^{11}C is too short. The softness of the radiation of ^{14}C, however, necessitates the use of extremely thin-walled counters, or preferably the introduction of the sample into the counter, in gaseous form.

A calcium isotope with a half-life of 180 days has been produced [23] by the action of deuterons on calcium and of fast neutrons on scandium, and must, in consequence, be regarded as ^{45}Ca. Its β-rays are not unduly soft and it should therefore be very suitable as a tracer. The 2·5-hours calcium, which had been used for such purposes, was found to form a radioactive scandium and must therefore be considered as less suitable. Incidentally, the formation of the active scandium (57-mins. period, ^{49}Sc) shows that the 2·5-hours activity is due to ^{49}Ca, formed from the recently discovered, rare isotope ^{48}Ca.

Chlorine strongly absorbs slow neutrons and becomes radioactive with a period of 37 mins. By means of the thermo-diffusion method (see this vol., p. 153), J. W. Kennedy and G. T. Seaborg [24] prepared samples of chlorine in which the abundance of the heavy isotope was strongly reduced, and found that the intensity of the 37-mins. period was much reduced, too. This shows that the activity is to be assigned to ^{38}Cl. It is far too weak, however, to account for all the neutrons absorbed by chlorine, and it has been assumed for some time that most of the neutrons are captured by ^{35}Cl, forming an active ^{36}Cl of very long period. According to unpublished experiments by D. C. Grahame and H. Walke (quoted by Kennedy and Seaborg [24]), such an isotope, with a period of more than a year, has now been found, but no further information regarding its properties is as yet available.

Element 85.—D. R. Corson, K. R. MacKenzie, and E. Segrè [25] bombarded bismuth with energetic " artificial α-particles," *i.e.*, helium which had been accelerated to an energy of 32 m.v. by means of the Berkeley cyclotron. Bismuth seemed a particularly interesting target, since capture of an α-particle with subsequent emission of one or more neutrons (which, in heavy elements, is much more likely than the emission of protons) would lead to the formation of an isotope of element 85. The bombarded bismuth emitted α-

[23] H. Walke, F. C. Thompson, and J. Holt, *Physical Rev.*, 1940, **57**, 177.
[24] *Ibid.*, p. 843.   [25] *Ibid.*, **58**, 672.

and γ-rays and decayed with a half-life of 7·5 hours.   The carrier of this activity was found to evaporate from the bismuth on melting and could be collected on a water-cooled plate.

Numerous chemical experiments showed the characteristic properties of this substance and supported the view that it is an isotope of element 85.   Although it is a higher homologue of iodine, it is not precipitated by silver nitrate from a slightly nitric acid solution, with potassium iodide as a carrier.   It has quite marked metallic properties and a closer resemblance to its neighbour polonium than to iodine ; it can, however, be separated from polonium—for example, by precipitation with sulphur dioxide in 3N-hydrochloric acid, with tellurium as a carrier.   It resembles iodine in that it is concentrated in the thyroid of guinea pigs.[26]

Analysis of its radiation supported the assignment to this substance of the atomic number 85.   Two groups of α-particles are emitted, of 4·52 and 6·55 cm. range.   The different intensity of the groups, as well as other evidence, excludes the possibility that the two α-particles are emitted in succession by the same nucleus, and suggests a branching decay.   The longer of the two groups has very accurately the same range as the α-rays of actinium-C', a polonium isotope with the mass 211.   The authors therefore assume that the active isotope has the mass 211, formed from ^{209}Bi by capture of an α-particle and emission of two neutrons.*   Some of its nuclei decay into ^{207}Bi, by emission of an α-particle of 4·52-cm. range, while the others decay, by capture of a K-electron and emission of the corresponding X-rays (which have been identified) into actinium-C', which has a period of the order of 10^{-3} sec. and turns into stable ^{207}Pb with the emission of a 6·57-cm. α-ray.   If this picture is correct (which seems highly probable), then ^{207}Bi must have a life of at least a month, since no radiation attributable to it has been observed.

The chemical properties of element 85 are of particular interest in connexion with attempts to detect the presence of this element in Nature.   It is now clear that the methods used by E. Buch-Anderson[27] in his search for element 85 in the natural radioactive families would not have led to an enrichment of 85 in the fractions studied by him, and the negative result of his search is therefore no proof of the non-occurrence of the element.   W. Minder[28] obtained evidence for a β-radiation from radium-A, which he believes

[26] J. G. Hamilton and M. H. Soley, *Proc. Nat. Acad. Sci.*, 1940, **26**, 483.

[27] *Kgl. Danske Vid. Selskab., Math.-Fys. Medd.*, 1938, **16**, 5.

[28] *Helv. Physica Acta*, 1940, **13**, 144.

* The capture of an α-particle with 32 m.v. gives such a high excitation energy to the compound nucleus that even after the " evaporation " of one neutron enough energy is left to evaporate a second one.

to be of nuclear origin rather than secondary.   β-Decay of radium-A
($Z = 84$) would indeed result in the formation of element 85, but
no actual proof of the presence of this element is given.   H. Holubei
and Y. Cauchois [29] have also reported experiments which they
interpret as evidence of the existence of element 85 in the decay
products of radon.   A theoretical discussion concerning the
possible formation and presumable radioactive properties of element
85 is given in a paper by L. A. Turner.[30]

The discovery of a radioactive isotope of element 93 is reported,
together with some of its chemical properties, in the section on
nuclear fission (p. 11).

Nuclear Isomerism.—The number of papers upon this phenomenon
and the complexities encountered in its study are so great that a
comprehensive account is out of question.   Instead, it is proposed,
together with a short recapitulation of the essential features, to
discuss a few representative papers and to present a survey, in the
form of a table, of our present knowledge.

The term "nuclear isomerism" was introduced to describe the
fact that nuclei with identical mass and charge number (*i.e.*, nuclei
of the same isotope) may yet have different (radioactive) properties.
The difference between isomeric nuclei cannot be assumed to lie
in a different arrangement of their component particles (as in
isomeric molecules), since anything like a rigid structure inside a
nucleus seems incompatible with quantum theory.   Instead, it
is now generally assumed that the difference is essentially one in
energy content or, in other words, that we have to do with different
energy states of the same nucleus.   The lower one may be assumed
to be the ground state of this nucleus, and the upper one a "meta-
stable" excited state.   A nucleus in the upper state can get rid
of its excess energy, either by radiation (emission of a γ-ray) or by
giving it to one of the extranuclear electrons ("internal conver-
sion"), and thereby drop into the ground state.   In most cases
this will happen within a very small fraction of a second.   If,
however, the nucleus in a particular excited state has got a moment
of rotation which differs by several units * from that of the ground
state (and of any intermediate state), and if, at the same time, the
energy difference between the two states is not too large, then the
transition may be so highly "forbidden" that the life of the upper
state gets long enough to be observed and then we get isomerism.

[29] *Compt. rend.*, 1939, **209**, 39.
[30] *Physical Rev.*, 1940, **57**, 950.

* One unit = $h/2\pi$; h = the quantum of action.   According to quantum
theory, the moment of rotation of any system always changes by an integral
number of these units.

All cases of isomerism so far observed may be classified under one of the following headings :

(A) A metastable state decays into the stable ground state, with the emission of electrons and/or γ-rays and X-rays.

(B) A metastable state decays into the ground state, which in turn undergoes β-transformation (we shall take this term as including any transformation which leads to a neighbouring element, i.e., electron or positron emission from the nucleus, and K-electron capture).

(C) Both metastable state and ground state undergo β-transformation.

The following kinds of evidence indicate that an activity is due to an isomeric transition $(I.T.)$ in a stable isotope (case A) :

(1) Its production by a process which can give rise to stable isotopes only, of the element in question. The production of the 4·5-hours ^{115}In * (the asterisk indicating an excited state) by irradiating indium with X-rays of 1·5 m.v., reported last year, is the classical example. More recently, a 1·6-mins. activity has been excited in lead, with X-rays of the same energy.[31]

(2) Emission of the characteristic X-rays of the element in question. (In the case of a β-transition, the X-rays of one of the neighbouring elements would be emitted, if any.) These X-rays may be identified either by means of a crystal spectrograph or, much more easily, through their absorption in suitably chosen filters.

(3) Evidence from the energy spectrum of the electrons emitted. The absence of a continuous spectrum is not sufficient evidence in itself, since it might be a case of K-capture. If lines due to the ejection of both K- and L-electrons are observed, their energy difference may be used to ascertain the atomic number of the nucleus after the transition. From the intensity ratio of the lines it is possible to calculate the change in rotational moment which accompanies the transition.

L. W. Alvarez, A. C. Helmholz, and E. Nelson[32] studied the electron spectrum of the 6·7-hours cadmium isotope, which was known to emit silver X-rays, indicating its decay to silver. From the unusually high ratio of L- to K-conversion electrons, they concluded that the difference in momentum between this excited state of silver and the ground state should be 4 units; from this and from the energy of the state (obtained from the energy of the conversion electrons) they calculated that it should have a life of about 30 secs. Experiment showed this prediction to be surprisingly

[31] B. Waldman and G. B. Collins, *Physical Rev.*, 1940, **57**, 338.

[32] *Ibid.*, p. 660.

accurate, for the authors were able to extract, from the 6·7-hours cadmium, an active silver fraction with a half-life of 40 secs. In this way the β-spectrograph not only helps to identify isomeric transitions, but may even help to discover new ones.

Isomerism of either type B or type C will have to be assumed if two periods, in view of the way in which they are produced, have to be assigned to the same isotope. If the nucleus in its ground state is β-active, the isomeric state has the choice of either going to the ground state or undergoing β-transformation, and both processes will occur side by side. In all cases so far known, however, the probability of one of the two processes is found to be negligible compared with that of the other; we are therefore left with the two limiting cases B and C, as defined above.

Although in case B the β-rays are emitted from the ground state only, their decay curve is complex, since the decay of the nuclei in the ground state is partly compensated by the decay of the excited nuclei *into* the ground state. The decay is, in fact, indistinguishable from that of a mixture of two radioactive substances and does not even allow one to tell which of the two periods corresponds to the *I.T.* and which to the β-decay. Study of the β-ray spectrum again supplies valuable information : In case B, the continuous spectrum, due to the β-transition, remains the same throughout the decay ; if the two periods were due to two different β-active bodies, such a behaviour would be highly improbable. In addition, one often observes conversion electrons and γ-rays which decay with a single period, that of the isomeric state. Absorption experiments are, in general, accurate enough to find whether the β-spectra of the two periods are identical or not, and to observe the soft conversion electrons and/or the γ-rays associated with one of them, while a β-spectrograph permits one, in addition, to study the exact location of the electron lines and to apply the sort of argument which we have discussed under A. If *X*-rays are observable (they are sometimes masked by strong γ-rays) their identification as the characteristic *X*-rays of the element in question offers a simple and convincing proof of the *I.T.*

In several cases it has been possible, as reported last year, to separate the nuclei in the two isomeric states by a chemical procedure. This possibility exists only in case B, and depends on whether the active element can be made part of a suitable compound which either breaks up or is activated by the isomeric transition, so that the nuclei which have gone to the ground state may be separated chemically from the others. The two bromine periods of 18 mins. and 4·5 hours were the first to be separated in this

way.[33,34] Don C. DeVault and W. F. Libby[35] more recently investigated a large number of methods for the separation of the bromine isomers. They find that about 15% of the lower isomer refuses to be extracted even by the most effective methods, and suggest that this represents the fraction of isomeric nuclei decaying by emission of a γ-ray rather than by internal conversion, the recoil from the γ-quantum being too weak to disturb the molecule. Methods for the separation of isomers of tellurium and selenium were developed by G. T. Seaborg, J. J. Livingood, and J. W. Kennedy,[36] and by A. Langsdorf and E. Segrè,[37] respectively.

The element indium[38] is a veritable show-case of isomerism. Metastable states of both the stable indium isotopes ^{113}In and ^{115}In have been produced and their radiations have been studied. The β-active ^{114}In has a metastable state which decays into the ground state (case B), and ^{116}In shows two independent β-periods with different energy spectra (case C).

In the following table, col. 2 indicates the type of isomerism as defined at the beginning of this section. Col. 3 indicates on what

Table of Isomeric Nuclei.

Isotope.	Type.	Evidence.	Periods.	Ref.
^{49}Ca	B or C	1	30 mins. ($-$)	23
			2·5 hours ($-$)	
^{44}Sc	B	1, 2	4·1 hours ($\beta +$)	39
			52 hours ($I.T.$)	
^{51}Ti	B or C	1	2·9 mins. ($-$)	40
			72 days ($-$)	
^{52}Mn	C	1, 2	21 mins. ($\beta +$)	41
			6·5 days ($\beta +$)	
^{60}Co	B or C	1	11 mins. ($-$)	42
			5·5 years ($\beta -$)	
^{69}Zn	B	2	57 mins. ($\beta -$)	43
			13·8 hours ($I.T.$)	
$^{79 \text{ or } 81}$Se	B	2, 4	19 mins. ($\beta -$)	37
			1 hour ($I.T.$)	
^{80}Br	B	1, 2, 3, 4	18 mins. ($\beta -$)	33, 34, 35
			4·5 hours ($I.T.$)	
^{83}Kr	A	1, 2, 3	113 mins. ($I.T.$)	37
^{85}Sr	B ?	1, 2	70 mins. ($I.T.$?)	44
			66 days (K)	
^{87}Sr	A	1, 2, 3	2·7 hours ($I.T.$)	44
^{87}Y	B ?	1, 2	14 hours ($I.T.$?)	44
			80 hours (K)	
^{89}Zr	B ?	1, 2	4·5 mins. ($I.T.$?)	44
			78 hours ($\beta +$)	
$^{99 \text{ or } 101}$43	A *	2, 3	6·6 hours ($I.T.$)	45

[33] E. Segrè, R. S. Halford, and G. T. Seaborg, *Physical Rev.*, 1939, **55**, 321.
[34] Don C. DeVault and W. F. Libby, *ibid.*, p. 322.
[35] *Ibid.*, 1940, **58**, 688.   [36] *Ibid.*, **57**, 363.   [37] *Ibid.*, p. 105.
[38] J. L. Lawson and J. M. Cork, *ibid.*, p. 982.

* Listed as "A" because no β-transition from ground state has been found; it is, however, almost certainly β-unstable.

Table of Isomeric Nuclei (contd.)

Isotope.	Type.	Evidence.	Periods.	Ref.
^{104}Rh	B	1, 2	44 secs. (β −) 4·2 mins. (*I.T.*)	46
^{106}Ag	B or C	1	25 mins. (β +) 8·2 days (K ?)	47
$^{107 \text{ or } 109}$Ag	A	2, 3	40 secs. (*I.T.*)	32
$^{108 \text{ or } 110}$Ag	B or C	1	22 secs. (^{110}Ag, β −) 2·3 mins. (^{108}Ag, β −) 225 days (β −)	48
$^{?}$Cd	A ?	1	50 mins. (*I.T.* ?)	49
^{113}In	A	2, 3	105 mins. (*I.T.*)	38
^{114}In	B	1, 2	72 sec. (β −) 50 days (*I.T.*)	38
^{115}In	A	1, 2	4·5 hours (*I.T.*)	38
^{116}In	C	1, 2	13 secs. (β −) 54 mins. (β −)	38
^{127}Te	B	2, 4	9·3 hours (β −) 90 days (*I.T.*)	36
^{129}Te	B	2, 4	72 mins. (β −) 32 days (*I.T.*)	36
^{131}Te	B	4	25 mins. (β −) 1·2 day (*I.T.*)	36
^{134}Cs	C	1, 2	3 hours (β −) 1·7 year (β −)	50
$^{152 \text{ and } 154}$Eu	B or C	1	12 mins. 105 mins. 9·4 hours (β −) 1 year (β −)	51
$^{176 \text{ or } 177}$Lu	?	1	4 hours 6 days	52
^{180}Ta	?	1	14—21 mins. 8·2 hours (K)	53
$^{192 \text{ or } 194}$Ir	B or C	1	1·5 mins. (β − ?) 19 hours (β −) 60 days (β − ?)	54
^{197}Pt	B or C	1	18 hours (β − ?) 3·3 days (β − ?)	54
^{196}Au	?	1	13 hours (β − ?) 4—5 days (β − ?)	54
$^{\text{stable}}$Pb	A	1, 2	1·6 mins. (*I.T.*)	31

[39] H. Walke, *Physical Rev.*, 1940, **57**, 163.

[40] H. Walke, E. J. Williams, and G. R. Evans, *Proc. Roy. Soc.*, 1939, *A*, **171**, 360.

[41] J. J. Livingood and G. T. Seaborg, *Physical Rev.*, 1938, **54**, 391; A. Hemmendinger, *ibid.*, 1940, **58**, 929.

[42] F. A. Heyn, *Physica*, 1937, **4**, 160, 1224; J. J. Livingood and G. T. Seaborg, *Physical Rev.*, 1938, **53**, 847.

[43] *Idem, ibid.*, 1939, **55**, 457.

[44] L. A. DuBridge and J. Marshall, *ibid.*, 1940, **58**, 7.

[45] G. T. Seaborg and E. Segrè, *ibid.*, 1939, **55**, 808.

[46] B. Pontecorvo, *ibid.*, 1938, **54**, 542.   [47] M. L. Pool, *ibid.*, 1938, **53**, 116.

[48] J. J. Livingood and G. T. Seaborg, *ibid.*, 1938, **54**, 88.

[49] M. Dodé and B. Pontecorvo, *Compt. rend.*, 1938, **207**, 287.

[50] D. C. Kalbfell and R. A. Cooley, *Physical Rev.*, 1940, **58**, 91.

[51] K. Fajans and D. W. Stewart, *ibid.*, 1939, **56**, 625.

[52] G. Hevesy and H. Levi, *Nature*, 1936, **137**, 185.

[53] O. Oldenberg, *Physical Rev.*, 1938, **53**, 35.

[54] E. McMillan, M. D. Kamen, and S. Ruben, *ibid.*, 1937, **52**, 375.

kind of evidence the assignment is based : " 1 " on the way in which the activity is produced; " 2 " on the energy distribution of the emitted particles; " 3 " on identification of the characteristic X-rays; and " 4 " denotes that the two isomeric nuclei have been separated by chemical means. $\beta +$ and $\beta -$ after the period mean that the nucleus in question undergoes β-transformation, with the emission of a positron or an electron, respectively; K indicates K-electron capture, and $I.T.$ means isomeric transition. $(-)$ means that it is uncertain whether the electrons emitted are of nuclear origin or conversion electrons.

NEUTRONS.

The magnetic moment of free neutrons has now been measured with great accuracy [55] and found to be $1·93 \pm 0·02$ nuclear magnetons (one nuclear magneton $= 1/1840$ Bohr magneton). The result is very nearly what had been expected on the assumption that the magnetic moment of the deuteron is the sum of the moments of the proton and the neutron.

The method, which is similar to the one by which Rabi and his collaborators have determined the nuclear moments of many elements, is capable of very great accuracy. A beam of slow neutrons was " polarised " by passage through magnetised iron and then passed through a homogeneous magnetic field, upon which was superimposed a weak field the direction of which alternated at a high frequency. The homogeneous field causes the neutrons to precess like small gyroscopes. If the frequency of this precession happens to coincide with the frequency of the superimposed field, the precession becomes disturbed and the beam is depolarised. On emerging from this high-frequency treatment, the neutrons had to pass through a second slab of magnetised iron, which served as an analyser. The homogeneous field was gradually altered until a sudden change in the beam intensity indicated that depolarisation was taking place. In this way the rate of precession in a given field was measured, and from it the magnetic moment of the neutrons can immediately be calculated.

Diffraction phenomena affecting the scattering of slow neutrons have been studied by several authors. F. Rasetti [56] found that precipitated and carefully dried calcium carbonate had a molecular cross-section which was equal to the sum of the cross-sections of the component atoms. A crystal of calcite showed a cross-section less than one-third of that, while ground powders of various grain sizes gave intermediate values. The explanation is that a single

[55] L. W. Alvarez and F. Bloch, *Physical Rev.*, 1940, **57**, 111.
[56] *Ibid.*, **58**, 321.

crystal scatters only those neutrons whose de Broglie wave-length happens to fulfil the Bragg condition for reflection by a lattice plane, while the other neutrons pass through almost freely. In a powder, however, a neutron passes through many grains of different orientations; in addition, the Bragg condition is less selective in small grains. H. G. Beyer and M. D. Whitaker [57] found similar anomalies with crystals of iron, nickel, and quartz. Apart from the fundamental interest of these experiments, they are of practical importance in so far as they call for a redetermination of all those slow-neutron scattering cross-sections which have been measured with crystalline scatterers. (Capture of neutrons, and scattering of faster neutrons should not be affected by the crystalline structure.)

O. R. FRISCH.

[57] *Physical Rev.*, 1940, **57**, 976.

GENERAL AND PHYSICAL CHEMISTRY.

1. INTRODUCTION.

A VARIETY of topics is dealt with in this section of the Reports. In the first section there is a discussion of the forces of interaction between very simple molecules. Here there are now two lines of approach. By the use of wave mechanics it is possible to calculate fairly accurately these interactions, provided that the system is simple enough. On the other hand, valuable information can also be obtained from the statistical properties of a gas—in particular the deviations from the ideal gas laws. W. J. C. Orr has described and examined the results obtained by the two methods of approach.

Coming next to a more complicated problem, namely, the structure of molecules, there is now a great range of methods, each of which is almost indispensable to the others. In recent Reports, the contributions made by the study of infra-red and Raman spectra and electronic spectra have been described. This year L. E. Sutton shows how much the study of electron diffraction by vapours and the measurement of dipole moments have contributed to this field of research.

Photochemistry can now be regarded as a branch of chemical kinetics, as its relationship with the latter subject is very close. Accordingly the report on reaction mechanisms is confined exclusively to a discussion of recent work in this branch. There have been prolonged controversies in photochemistry, not only about the interpretation of results, but also about the validity of the results themselves. It is in a way unfortunate that the subject has often become clouded over in this manner. However, clarity is now beginning to appear, as it is realised that the behaviour of photochemically excited molecules is indeed much more complex than has hitherto been suspected. Long-held dogmas have had to be abandoned—often to the mutual satisfaction of rival theories. M. Ritchie consequently gives an account of the efforts made to probe further into these reactions and bring harmony even at the expense of complexity into the subject.

Classical colloid chemistry is a subject often shunned by the more theoretical of physical chemists, probably because of its rather qualitative nature. There is, however, a vigorous revival taking place which must be chronicled. A. S. C. Lawrence describes in some detail the clarification of ideas in many parts of this branch of chemistry.   H. W. M.

2. INTERMOLECULAR ENERGIES.

Explicit determinations of the potential energy of a pair of molecules as a function of their distance apart may in principle be obtained either from direct quantal calculations or from inductive analyses of the thermodynamic and kinetic behaviour of actual physical systems. Limiting our field in this review to a discussion of the interactions of the rare-gas atoms and chemically saturated, non-polar, spherically symmetrical molecules, we shall summarise the methods which have had practical success in this aim and describe current developments.

(a) *Direct Calculations.*—The calculation of the interatomic energies of particles, containing more than one electron, involves in practice approximations concerning (a) the analytic form of the wave function, Ψ, or related electron distribution ρ, assumed for the separate particles, and (b) the analytic behaviour of these functions as the particles are brought together. Among the systems here considered Ψ has been accurately calculated in the case of helium only.[1] The values of Ψ (or ρ) for more complicated atoms have been obtained either from the Fermi–Thomas[2] statistical model or from some modification of the Slater[3] central field model. The Fermi–Thomas method represents the atom as a nucleus surrounded by an electron gas in which the number of electrons in any element of phase space h^3 is limited, in accordance with the Pauli principle, to two of opposite spin. In this way approximate, smoothed-out electron distribution curves are obtained. In the Slater method the electrons of an atom are considered to be moving independently in the central field of the nucleus. The total wave function Ψ for a system of N electrons may then be expressed as a determinant whose N^2 terms are single-electron ψ, mutually orthogonal, and normalised functions of the space and spin coordinates. Such a form is antisymmetrical in the electrons, as required by the Pauli principle, and includes exchange of the electrons among the available eigen-functions. Numerical methods of calculating these satisfying the Schroedinger equation for

[1] E. A. Hylleraas, *Z. Physik*, 1928, **48**, 469; **51**, 150; 1929, **54**, 347; 1930, **65**, 209; A. F. Stevenson and M. F. Crawford, *Physical Rev.*, 1938, **54**, 275.

[2] L. H. Thomas, *Proc. Camb. Phil. Soc.*, 1927, **23**, 542; E. Fermi, *Z. Physik*, 1928, **48**, 73. A description of the use of this method and a bibliography are given by H. Hellmann, "Einführung in die Quantenchemie," Chap. 1.

[3] J. C. Slater, *Physical Rev.*, 1929, **34**, 1293; also E. U. Condon and G. H. Shortley, "The Theory of Atomic Spectra," Chap. 6.

particular atoms have been developed by D. R. Hartree[4] and V. Fock.[5]

As two particles are brought together, their wave functions are increasingly influenced by each other's presence, and the potential energy of the system alters accordingly. On the statistical model this energy is composed of the mutual electrostatic attractions of electron clouds and nuclei, the exchange energy of the electrons, and the repulsion due to the kinetic energy of the electrons, the last term predominating. Calculations have been carried out for systems having completed electron shells by W. Lenz,[6] H. Jensen,[7] P. Gombas,[8] and others. Since the Fermi–Thomas distribution falls off too slowly at large distances, these calculations tend to give too large a repulsive potential. H. Hellmann[9] has shown, however, that the statistical method yields good results in the case of two helium atoms when wave-mechanical distributions are employed. Hence, although this method cannot lead to high precision calculations of repulsive energy, it can provide useful approximations for systems too complicated to be treated wave-mechanically.

Three general approximation methods are available by which the quantum-mechanical energy of two interacting neutral atoms may be calculated, viz., (a) the generalised perturbation method of Heitler and London, (b) the perturbation method neglecting electron exchange between the atoms, and (c) the variation method. In the first method a wave function, having a determinantal form, containing ψ for the electrons of both atoms is formed, and the Schroedinger equation is solved for the potential energy by the approximation methods first developed by W. Heitler and F. London[10] and Y. Sugiura[11] for the hydrogen molecule. In the case of atoms having rare-gas configurations this method yields a repulsive potential at all distances. A calculation accurate to 1 or 2% for the case of two helium atoms has been made by J. C. Slater,[12]

[4] *Proc. Camb. Phil. Soc.*, 1928, **24,** 89, 111.

[5] *Z. Physik*, 1930, **61,** 126; **62,** 795. A list of references on this method up to 1936 is given by H. Hellmann, *op. cit.*, Chap. 3. Further references are : D. R. Hartree and W. Hartree, *Proc. Roy. Soc.*, 1938, **164,** *A,* 167; **166,** *A,* 450; *Proc. Camb. Phil. Soc.*, 1938, **34,** 550; D. R. Hartree, W. Hartree, and B. Swirles, *Phil. Trans.*, 1939, **238,** *A,* 229; A. F. Stevenson, *Proc. Roy. Soc.*, 1937, **160,** *A,* 588; *Physical Rev.*, 1939, **56,** 586; M. F. Manning and L. Goldberg, *Physical Rev.*, 1938, **53,** 662; R. L. Mooney, *ibid.*, 1939, **55,** 557; W. J. Yost, *ibid.*, 1940, **58,** 556; A. O. Williams, *ibid.*, p. 723.

[6] *Z. Physik*, 1932, **77,** 713.

[7] *Ibid.*, p. 722; 1936, **101,** 141, 164.

[8] P. Gombas and T. Neugebauer, *ibid.*, 1934, **89,** 480; P. Gombas, *ibid.*, **92,** 796; **93,** 378; cf. also R. P. Bell, *Proc. Roy. Soc.*, 1940, **174,** *A,* 504.

[9] *Z. Physik*, 1933, **85,** 180. [10] *Ibid.*, 1927, **44,** 455. [11] *Ibid.*, **45,** 488.

[12] *Physical Rev.*, 1928, **32,** 349; cf. also N. Rosen, *ibid.*, 1931, **38,** 255.

using analytic wave functions. W. E. Bleick and J. E. Mayer [13] treat the case of two neon atoms, using approximate Hartree wave functions. The results of both these calculations are well represented by a simple exponential law, $B(R) = A\exp.(-aR)$. Such a relation is also suggested as a limiting law by calculations on the exchange forces between hydrogen-like atoms and K, L, M, and N electron shells,[14, 15] but at normal equilibrium distances it is found that much more complicated expressions are involved. A recent approximate method of reducing this many-electron problem to a number of single-electron problems has been suggested by M. F. Mamotenko and A. A. Schuchowitzky.[16] This treatment introduces special orthogonalisation principles designed to conserve the Pauli principle and to reduce to a minimum the contribution of the exchange integrals. Using J. C. Slater's atomic wave functions,[17] the repulsive potentials of pairs of hydrogen and helium atoms are obtained in fair agreement with more elaborate methods.[11, 12]

In the perturbation method the Hamiltonian expression for the interaction energy, H, is averaged over all the unperturbed states of the separate systems. For the case where the energy levels E_n are non-degenerate, the expansion, as far as the second approximation, is as follows :

$$\phi = \int \psi_n H \bar{\psi}_n d\tau + \overset{i}{\underset{i \neq k}{\Sigma}} \int \{[\psi_i H \psi_k]^2/(E_i - E_k)\} d\tau$$

In the variation method, suitable analytic forms of Ψ are chosen containing arbitrary parameters, which then are varied to make the expression $\phi = \int \Psi H \bar{\Psi} d\tau / \int \Psi \bar{\Psi} d\tau$ a minimum. The energy so calculated will provide an upper limit to the experimental value even when the central field Ψ is used, since the latter neglects correlations in the relative motion of electrons. In the case of non-polar, spherically symmetrical molecules the first-order perturbation energy is zero. For unsymmetrical molecules such as hydrogen,[18] however, the first-order mutual quadruple interaction survives and gives attractive and repulsive potentials depending

[13] *J. Chem. Physics*, 1934, **2**, 252.

[14] A. Unsöld, *Z. Physik*, 1927, **43**, 563.

[15] H. Brück, 1928, **51**, 707; also V. Zdanow, A. Erschow, and G. Galachow, *ibid.*, 1935, **94**, 241.

[16] *Acta Physicochim. U.R.S.S.*, 1938, **9**, 803; M. F. Mamotenko, *ibid.*, 1939, **11**, 225; A. A. Schuchowitzky, *ibid.*, 1935, **2**, 81.

[17] *Physical Rev.*, 1930, **36**, 57.

[18] F. London, *Z. physikal. Chem.*, 1931, *B*, **11**, 222; H. S. W. Massey and R. A. Buckingham, *Proc. Roy. Irish Acad. Sci.*, 1938, **45**, *A*, 31; J. K. Knipp, *Physical Rev.*, 1938, **53**, 734; K. Cohen and H. C. Urey, *J. Chem. Physics*, 1939, **7**, 157.

on the relative orientation of the molecules, the average energy over all orientations being zero. For molecules with low moments of inertia, such as those considered here, this effect would never be physically appreciable but it is possibly significant for the analysis of kinetic data involving highly asymmetrical molecules.

The second-order perturbation calculation yields results equivalent to a variation calculation, the energy so calculated corresponding always to an attractive potential. At distances apart of two or more molecular diameters it is permissible to neglect electron exchange between the particles and to simplify the calculation by expanding the Coulomb electrostatic energy in a Taylor's series in the internuclear distance R. The successive terms in the expansion, varying as R^{-3}, R^{-4}, etc., give rise to the dipole–dipole, dipole–quadrupole, etc., energies, which vary as R^{-6}, R^{-8}. A detailed review of the calculation of these van der Waals forces up to 1939 has been made by H. Margenau,[19] and only a brief summary of the results will be given here. The first successful calculations applicable to a number of atoms and molecules were made by F. London,[20] who, using a perturbation method, obtained an expression for the dipole–dipole energy, in terms of the constants of the optical dispersion formula, for the interacting particles. A more general, but less accurate expression, also due to F. London,[18] involves the ionisation potentials and polarisabilities of the reacting particles. H. Margenau [21] has extended this method to calculate approximately the corresponding dipole–quadrupole energies. These calculations and those of R. A. Buckingham [22] agree in showing that the R^{-8} energy terms contribute about 20% to the total van der Waals potential at the energy minimum, and that the R^{-10} term can in general be neglected. Variation calculations employing progressively more adequate wave functions have been considered by J. C. Slater and J. G. Kirkwood,[23] J. G. Kirkwood,[24] J. P. Vinti,[25] H. Hellmann,[26] and R. A. Buckingham.[22] The results of these calculations have been discussed by J. K. Knipp [27] in relation to his own more general treatment. Knipp uses the central field approximation with Hartree eigen-functions to calculate the dipole–dipole energies of argon atoms. A significant feature of the calculations is that 98% of this energy is contributed by the outer electron shells.

Special attention has been devoted to calculating the van der

[19] *Rev. Mod. Physics*, 1939, **11**, 1.   [20] *Z. Physik*, 1930, **63**, 245.
[21] *J. Chem. Physics*, 1938, **9**, 896.   [22] *Proc. Roy. Soc.*, 1937, **160**, A, 113.
[23] *Physical Rev.*, 1931, **37**, 682.   [24] *Physikal. Z.*, 1931, **33**, 57.
[25] *Physical Rev.*, 1932, **41**, 813.
[26] *Acta Physicochim. U.R.S.S.*, 1935, **2**, 273.
[27] *Physical Rev.*, 1939, **55**, 1244.

Waals energy of two helium atoms. The most accurate calculations of the R^{-6} coefficient are those of H. R. Hassé,[28] who, using accurate Hylleraas $^1\Psi$, obtains the value $1\cdot368 \times 10^{-12}$ erg A.^{6}. The successive R^{-8} and R^{-10} coefficients have been calculated approximately by H. Margenau [29] and by G. H. Page.[30] While the theoretical position remained as described above, it was not permissible without further analysis to add together the calculated " exchange " repulsive potential and the van der Waals potentials, calculated with neglect of exchange, to obtain the potential curve in the neighbourhood of the minimum, as was frequently assumed. H. Margenau,[31] however, calculates the second-order exchange energy at the minimum and finds that, although this forms a very important contribution in the case of two hydrogen atoms,[32] yet it yields only a small attractive potential in the case of two helium atoms. It is considered probable that the relative importance of this term will be much less for heavier atoms. The best available self-consistent quantum-mechanical calculation of the interaction energy of two helium atoms, valid over a wide range of internuclear distances, is given by the following expression, which combines J. C. Slater's calculation [12] of the repulsive with H. Margenau's calculations [31] of the attractive potentials :

$$\phi = [770 \exp.(-4\cdot60R) - 560 \exp.(-5\cdot33R) - 1\cdot39/R^6 - 3\cdot0/R^8] \times 10^{-12} \text{ erg} \quad . \quad . \quad (1)$$

(b) *Thermodynamic Data.*—The analysis of thermodynamic data in terms of force fields implies the existence of an adequate statistical description of the system involved. Although useful supplementary information can be deduced from the properties of solid and liquid phases, the greatest detail is obtained at present from gas-phase data. Owing to the work of J. E. Mayer,[33] it is now possible to expand the classical configuration integral which occurs in the expression for the Helmholtz free energy of a gas of N molecules confined in a volume v, as a power series in the density N/v, the successive terms representing the interaction of molecules in groups of two, of three, and so on. The combinatory analysis has been discussed and clarified by various authors.[34] The first

[28] *Proc. Camb. Phil. Soc.*, 1930, **26**, 542; 1931, **27**, 66; T. D. H. Baber and H. R. Hassé, *ibid.*, 1937, **33**, 253.

[29] *Physical Rev.*, 1931, **38**, 747.

[30] *Ibid.*, 1938, **53**, 426.   [31] *Ibid.*, 1939, **56**, 1000.

[32] H. Hellmann and K. W. Majewski, *Trans. Faraday Soc.*, 1937, **33**, 43.

[33] *J. Chem. Physics*, 1937, **5**, 67; J. E. Mayer and P. G. Ackermann, *ibid.*, p. 74; J. E. Mayer and S. F. Harrison, *ibid.*, 1938, **6**, 87; S. F. Streeter and J. E. Mayer, *ibid.*, 1939, **7**, 1025; J. E. Mayer, *J. Physical Chem.*, 1939, **43**, 71.

[34] M. Born, *Physica*, 1937, **4**, 1034; M. Born and K. Fuchs, *Proc. Roy. Soc.*, 1938, **166**, *A*, 391; B. Kahn and G. E. Uhlenbeck, *Physica*, 1938, **5**, 399.

three terms of the equation of state derived therefrom are as follows : [35]

$$Pv = RT\left[1 - \frac{2\pi N}{3RTv} \int_0^\infty e^{-\phi(R)/kT} \frac{d\phi(R)}{dR} R^3 dR - \right.$$

$$\left. \frac{2\pi N^2}{3RTv^2} \int_0^\infty e^{-\phi(R)/kT} g_2(R) \frac{d\phi(R)}{dR} R^3 dR + \ldots \right] \quad . \quad . \quad (2)$$

$\phi(R)$ being the intermolecular potential and $g_2(R)$ an integral due to the simultaneous interaction of three molecules. Since the present accuracy of the experimentally measured virial coefficients [B and C in the expression, $Pv = RT(1 + B/v + C/v^2)\ldots$] is too low to permit a direct determination of $\phi(R)$ by inversion of the above integrals,[36] these must be integrated directly or numerically for particular analytic $\phi(R)$ whose unknown parameters are to be fixed by comparing the calculated and experimental behaviour of B and C as functions of the temperature T. The first detailed analyses of this kind were carried out by J. E. Lennard-Jones,[37] who employed the bi-reciprocal function, $\phi = -\mu/R^m + \nu/R^n$. With $m = 6$ it was found that equally good fits were obtained with values of n varying from 8 to 14. The experimental sublimation energies and interatomic distances of the crystals were used to fix these constants more precisely.[37,38]   J. Corner[39] has shown, in the case of neon and argon, that both crystal and virial data are well represented by unique potential functions of this kind. The effect of exponential repulsive potentials, which are suggested by quantum theory, has been examined by R. A. Buckingham,[40] J. A. Wasastjerna,[41] and others.[42]   A calculation of the third virial coefficients for a number of gases, using a bi-reciprocal potential curve with $n = 12$, has been carried through by J. de Boer and A. Michels[35,43] and, although laborious, forms a useful check on the constants of the potential curve calculated from the second virial coefficients.

[35] J. G. Kirkwood, *J. Chem. Physics*, 1935, **3**, 300; J. de Boer and A. Michels, *Physica*, 1939, **6**, 97.

[36] S. C. Collins and F. G. Keyes, *J. Physical Chem.*, 1939, **43**, 5; R. E. A. C. Paley and N. Wiener, *Amer. Math. Soc. Coll. Pub.*, 1934, **19**, Chap. 3.

[37] *Proc. Physical Soc.*, 1931, **43**, 461; *Physica*, 1937, **4**, 941. A further review of this work is contained in R. H. Fowler and E. A. Guggenheim's "Statistical Thermodynamics," Camb. Univ. Press, 1939, Chap. 7.

[38] M. E. Hobbs, *J. Chem. Physics*, 1939, **7**, 318.

[39] *Trans. Faraday Soc.*, 1939, **35**, 711.

[40] *Proc. Roy. Soc.*, 1938, **168**, A, 264.

[41] *Soc. Sci. Fenn. Phys. Math.*, 1932, **6**, Nos. 18—22; 1935, No. 20; *Phil. Trans.*, 1938, **237**, A, 105.

[42] J. G. Kirkwood and F. G. Keyes, *Physical Rev.*, 1931, **37**, 832; K. Herzfeld, *ibid.*, 1937, **52**, 374.

[43] *Physica*, 1938, **5**, 945.

Joule–Thomson coefficients,[36, 44] which can now be measured to an accuracy of 1%, provide a second convenient source of thermodynamic data for force field analysis. J. O. Hirschfelder, R. B. Ewell, and J. R. Roebuck[45] calculate potential curves taking account of quantum corrections for helium, neon, and argon by using such measurements. Further similar inductive analyses have been made by W. Wen-Po[46] and J. Corner.[47] A third source from which sufficiently accurate virial coefficients can be calculated is provided by the measurement of sound velocities in gases, a field which is being developed by A. van Itterbeek and his co-workers.[48] This method is especially useful in that it considerably extends the present temperature range of data available.

For gases such as hydrogen, deuterium, and especially helium, at low temperatures where the de Broglie wave-length $\lambda = h/\sqrt{mkT}$ is of the order of magnitude of a molecular diameter, the above-described classical treatment is no longer adequate.[49] The influence of the mutual field $\phi(R)$ of a pair of particles of mass m, energy E, and angular momentum $(h/2\pi)\sqrt{l(l+1)}$ on their relative motion is obtained by solving the radial wave equation[50]

$$\mathrm{d}^2(R\psi)/\mathrm{d}R^2 + [\kappa^2 - (4\pi^2m/h^2)\phi(R) - l(l+1)/R^2](R\psi) = 0 \quad . \quad (3)$$

where $\kappa^2 = 4\pi^2mE/h^2$, the proper asymptotic solution of which is $\psi = R^{-1}\sin(\kappa R - \tfrac{1}{2}l\pi + \delta_l)$. In terms of the phases δ_l, thus defined, and the discrete energy levels E_n and weights g_n of the function $\phi(R)$, the second virial coefficient is[51]

$$B(T) = -\frac{Nh^3}{16(\pi mkT)^{3/2}}\left\{\varepsilon + \frac{8}{\pi}\sum_l(2l+1)\int_0^\infty \frac{\mathrm{d}\delta_l}{\mathrm{d}\kappa}e^{-\kappa^2/\kappa_0^2}\ \mathrm{d}\kappa + 8\sum_n g_n e^{E_n/kT}\right\} \quad . \quad . \quad (4)$$

When the atoms contain an even number of elementary particles

[44] J. R. Roebuck and H. Osterberg, *J. Chem. Physics*, 1940, **8**, 627 (contains a complete list of references to their earlier work).

[45] *Ibid.*, 1938, **6**, 205; J. O. Hirschfelder and W. E. Roseveare, *J. Physical Chem.*, 1939, **43**, 15.

[46] *Phil. Mag.*, 1939, [vii], **26**, 225.

[47] *Trans. Faraday Soc.*, 1940, **36**, 781.

[48] A. van Itterbeek and P. Mariens, *Physica*, 1938, **5**, 153; 1940, **7**, 125; A. van Itterbeek and O. van Paemel, *ibid.*, 1938, **5**, 593, 845; A. van Itterbeek and L. Thys, *ibid.*, pp. 640, 889; A. van Itterbeek, P. de Bruyn, and P. Mariens, *ibid.*, 1939, **6**, 511.

[49] E. Wigner, *Physical Rev.*, 1932, **40**, 749; J. C. Slater, *ibid.*, 1931, **38**, 237.

[50] H. Faxen and J. Holtsmark, *Z. Physik*, 1927, **45**, 307; N. F. Mott and H. S. W. Massey, "The Theory of Atomic Collisions," 1933, Chap. 2; K. Schäfer, *Z. physikal. Chem.*, 1937, *B*, **36**, 85; *B*, **38**, 187.

[51] L. Gropper, *Physical Rev.*, 1936, **50**, 963; 1937, **51**, 1108; E. Beth and G. E. Uhlenbeck, *Physica*, 1937, **4**, 915; B. Kahn, *Diss.*, Utrecht.

(Bose–Einstein statistics), $\varepsilon = +1$, the summations are taken twice over even values of l, whereas, when they contain an odd number (Fermi–Dirac statistics), $\varepsilon = -1$, and the summations are taken twice over odd values of l. At high temperatures these expressions converge to the classical one. Series expansions have been developed for use in this region.[52] At low temperatures, however, the δ_l and E_n must be calculated numerically for particular forms of $\phi(R)$. Such calculations have been made in the case of helium by H. S. W. Massey and R. A. Buckingham,[53] who use a Slater–Kirkwood [23] potential; by L. Gropper,[54] who adds to this potential the R^{-8} and R^{-10} terms calculated by H. Margenau [29] and concludes, from a comparison of the experimental [55] and the calculated values of $B(T)$ in the liquid helium temperature range, that the true potential curve must lie between these two; and finally, by J. de Boer and A. Michels,[56] who obtain close agreement with experiment using a bi-reciprocal potential curve determined by inductive analysis from high-temperature helium virial data.[43] They further find that this curve gives somewhat closer agreement than is obtained by using the most recent purely theoretical curve already mentioned, *viz.*, equation (1).[31] The present degree of concordance between the best theoretical and inductively determined potential curves for helium is shown in the figure.

Although it is possible to obtain potential curves accurate over a wide range of values of R by the inductive analysis of thermodynamic data on gases covering an extensive temperature range (and thus a wide range of collision diameters), yet similar analyses of the available data on condensed phases, which are restricted to much more limited density ranges, give precise information appropriate only to the region of the potential minimum.

An accurate statistical theory of the liquid phase has not yet been obtained. The " statistical cage " model has been improved by the explicit introduction of actual intermolecular potentials by J. E. Lennard-Jones and A. F. Devonshire,[57] who successfully calculate various physical properties and constants of simple

[52] J. G. Kirkwood, *Physical Rev.*, 1933, **44**, 31; G. E. Uhlenbeck and E. Beth, *Physica*, 1936, **3**, 729.

[53] *Proc. Roy. Soc.*, 1938, **168**, *A*, 378; **169**, *A*, 205.

[54] *Physical Rev.*, 1939, **55**, 1095.

[55] W. H. Keesom and H. H. Kraak, *Physica*, 1935, **2**, 37; W. H. Keesom and W. K. Walstra, *ibid.*, 1939, **6**, 1146.

[56] *Ibid.*, p. 409.

[57] *Proc. Roy. Soc.*, 1937, **163**, *A*, 53; **165**, *A*, 1; 1939, **169**, *A*, 317; **170**, *A*, 464; A. F. Devonshire, *ibid.*, 1940, **174**, *A*, 102; J. E. Lennard-Jones, *Proc. Physical Soc.*, 1940, **52**, 729; J. E. Lennard-Jones and J. Corner, *Trans. Faraday Soc.*, 1940, **36**, 1156; W. J. Archibald, *Physical Rev.*, 1939, **56**, 926.

liquids in terms of the parameters of the potential curves. Inversely, such data can be interpreted on the basis of this model to give information regarding the force fields of the molecules concerned. Recent developments, both theoretical and experimental,[58] now enable one to calculate the atomic distribution function, $g(R)$, for quasi-monatomic liquids from the experimental X-ray scattering
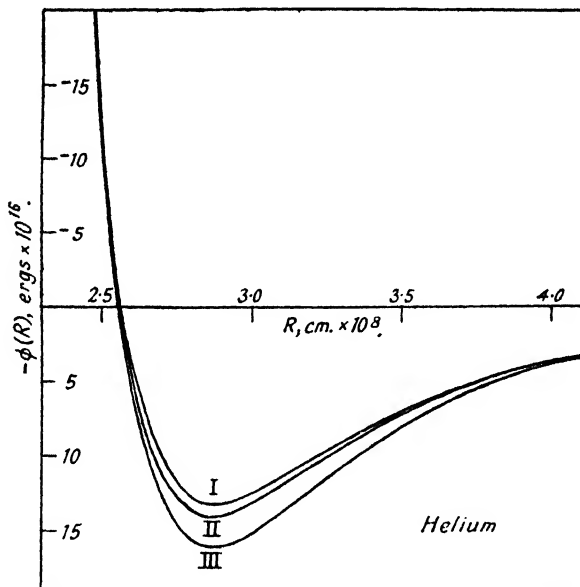
I. $\phi(R) = \left(\dfrac{439}{R^{12}} - \dfrac{1 \cdot 52}{R^6}\right) \times 10^{-12}$. (Ref. 45.)

II. $\phi(R) = \left(\dfrac{444}{R^{12}} - \dfrac{1 \cdot 58}{R^6}\right) \times 10^{-12}$. (Ref. 43.)

III. $\phi(R) = \left(770 e^{-4 \cdot 60 R} - 560 e^{-5 \cdot 33 R} - \dfrac{1 \cdot 39}{R^6} - \dfrac{3 \cdot 0}{R^8}\right) \times 10^{-12}$. (Ref. 31.)

curves, so that it is possible by combining various purely experimental data to determine the force fields by induction. J. H. Hildebrand [59] uses the relation

$$2\pi N^2 \int_0^\infty \phi(R) g(R) R^2 \mathrm{d}R = Ev$$

(where v and E are the molal volume and the energy of evaporation), in conjunction with the experimental $g(R)$ curves at a series of

[58] B. E. Warren and N. S. Gingrich, *Physical Rev.*, 1934, **46**, 368; B. E. Warren, *J. Appl. Physics*, 1937, **8**, 645.

[59] *J. Chem. Physics*, 1933, **1**, 817; 1939, **7**, 1; J. H. Hildebrand, H. R. R. Wakeham, and R. N. Boyd, *ibid.*, 1939, **7**, 1094.

temperatures,[60] to derive the constants of a bi-reciprocal potential in the case of liquid mercury. Further analyses of this kind on argon [61] and other similar simple liquid systems would provide information on the important question of the structure of liquids as well as on intermolecular potentials.[62]

A rigorous statistical theory of the thermodynamic behaviour of crystals is being developed and applied to calculate various physical properties, notably the melting points and behaviour under strain in terms of a general intermolecular force field, by M. Born and his co-workers.[63] The full development of this work, particularly in its application to the solid rare-gas atoms, should lead to accurate determinations, by inductive analysis, of the position and, in particular, the curvature of the potential curves in the vicinity of the minimum. Calculations of this kind, but based on the assumption of a Debye spectrum of frequencies, have already been made by various workers,[64] who obtain fair agreement with experiment by using force fields otherwise determined.

(c) *Kinetic Data.*—In a recent treatise S. Chapman and T. G. Cowling [65] have described in detail the classical derivation of the molecular distribution law for non-uniform gases in its fully developed form, which is mainly due to D. Enskog,[66] S. Chapman,[67] and D. Burnett.[68] In terms of this law, such free-path phenomena as the viscosity, thermal conductivity, and molecular and thermal diffusion of simple gases can be treated on the basis of certain simple molecular models. A general treatment of all these phenomena can at present best be given in terms of a law of mutual molecular repulsion, *viz.*, $\phi = \nu/R^n$. On this model, the temperature variation of the viscosity, η, of a gas should be $\eta/\eta_0 = (T/T_0)^S$, where $S = \frac{1}{2} - 2/n$. The actual values of n obtained, which vary from

[60] R. N. Boyd and H. R. R. Wakeham, *J. Chem. Physics*, 1939, **7**, 958.

[61] A. Eisenstein and N. S. Gingrich, *Physical Rev.*, 1940, **58**, 307; K. Lark-Horovitz and E. P. Miller, *Nature*, 1940, **146**, 459.

[62] C. N. Wall, *Physical Rev.*, 1938, **54**, 1062; C. A. Coulson and G. S. Rushbrooke, *ibid.*, 1939, **56**, 1216; J. Corner, *Proc. Physical Soc.*, 1940, **52**, 764.

[63] *J. Chem. Physics*, 1939, **7**, 591; *Proc. Camb. Phil. Soc.*, 1940, **36**, 160; M. Born and R. D. Misra, *ibid.*, pp. 173, 466; M. Born and R. Furth, *ibid.*, p. 454; *Nature*, 1940, **145**, 741.

[64] K. Herzfeld and M. Goeppert-Mayer, *Physical Rev.*, 1934, **46**, 995; G. Kane, *J. Chem. Physics*, 1939, **7**, 603; W. Wen-Po, *Phil. Mag.*, 1936, [vii,] **22**, 49, 281; 1937, **23**, 33; **24**, 466; 1938, **25**, 111.

[65] "The Mathematical Theory of Non-uniform Gases," Camb. Univ. Press, 1939.

[66] Diss., Upsala, 1917; *Svensk Vet. Akad. Arkiv. Mat. Ast. Fys.*, 1921, **16**, 1.

[67] *Phil. Trans.*, 1916, **216**, A, 279; 1917, **217**, A, 115.

[68] *Proc. Lond. Math. Soc.*, 1935, **39**, 385; **40**, 382; *Proc. Camb. Phil. Soc.*, 1937, **33**, 359, 363.

13·5 for helium to 6·4 for argon, indicate the much greater inter-penetration of the electron shells that occurs at comparable temperatures in collisions involving the lighter atoms.   A slight trend of n with temperature is due to the approximate nature of the potential law assumed.   A further indication that a more elaborate model is required is the fact that the average values of n_{12} for pairs of gases, obtained from the analyses of diffusion coefficients, are uniformly lower than the means of the individual values of n_1 and n_2 determined from viscosity measurements.   In the case of viscosity, the experimental data have also been analysed in terms of various other models, the most general of which are those of J. E. Lennard-Jones,[69] who combines a repulsive potential with a R^{-2} attractive potential, and H. R. Hassé and W. R. Cook,[70] who use a R^{-4} attractive term.   The Lennard-Jones model gives a two-constant formula, which represents the experimental data accurately over a wider range of temperature than the simpler model, but diverges at low temperatures, as would be expected since, in this region, in addition to quantum effects in the cases of hydrogen and helium, the contribution of the attractive potential is important.[71] A summary of the experimental and theoretical work in this field up to 1939 is given by S. Weber.[72]   A. van Itterbeek and W. H. Keesom [73] have initiated a further new series of experimental measurements [74] on gas viscosities.

Extensive measurements on the thermal diffusion of gases, which prove to be convenient and accessible sources of force-field data, have been carried out by T. L. Ibbs and his co-workers.[75] Moreover, wide prospects now exist for the further development of this field in the use of isotopic mixtures, since the mathematical problems involved in the interpretation of the data are thereby much simplified.[76]   Theoretical expressions for the thermal diffusion

[69] *Proc. Roy. Soc.*, 1924, **106**, *A*, 441; 1925, **107**, *A*, 157; J. E. Lennard-Jones and W. R. Cook, *ibid.*, 1926, **112**, *A*, 214.

[70] *Proc. Roy. Soc.*, 1929, **125**, *A*, 196; also W. Wen-Po, *Phil. Mag.*, 1938, [vii], **25**, 865.

[71] A. van Itterbeek and O. van Paemel, *Physica*, 1938, **5**, 1009.

[72] *Ibid.*, 1939, **6**, 562.

[73] *Ibid.*, 1933, **1**, 128; 1935, **2**, 97; 1938, **5**, 257.

[74] W. H. Keesom and G. E. Macwood, *ibid.*, p. 749; A. van Itterbeek and A. Claes, *ibid.*, p. 938; W. H. Keesom and P. H. Keesom, *ibid.*, 1940, **7**, 29; A. van Itterbeek and O. van Paemel, *ibid.*, p. 273; also A. B. van Cleave and O. Maass, *Canadian J. Res.*, 1935, **12**, 57; **13**, 384.

[75] T. L. Ibbs, *Physica*, 1937, **4**, 1133 (bibliography up to 1937); B. E. Atkins, R. E. Bastick, and T. L. Ibbs, *Proc. Roy. Soc.*, 1939, **172**, *A*, 142; A. A. Hirst and G. E. Harrison, *ibid.*, **169**, *A*, 573; R. E. Bastick, H. R. Heath, and T. L. Ibbs, *ibid.*, **173**, *A*, 543.

[76] S. Chapman, (a) *Phil. Mag.*, 1917, **34**, 146; 1919, **38**, 182; (b) *Nature*, 1940, **146**, 607.

coefficients of isotopic mixtures have been made, to the same degree of accuracy as the present viscosity calculations, for different molecular models, by R. C. Jones,[77] and the relative accuracy of these models is estimated by comparing the measured thermal diffusion coefficients, for a given temperature interval, with theoretical values calculated from the experimental viscosities in the same interval. Such intercomparisons for isotopic mixtures of methane [78] and of neon [79] indicate that this method is rather sensitive to the proper form of molecular field and may prove a valuable additional method of determining the actual constants.[76b, 77, 80] A further important application of these calculations of thermal diffusion coefficients lies in their connexion with K. Clusius and G. Dickel's method [81] of separating isotopes. Theoretical calculations [82] of the efficiency of such a system for separating the isotopes of carbon, methane being used, have recently been confirmed by experiment.[83]

The generalisation of the classical treatment of D. Enskog and S. Chapman to include quantum statistics has been made by E. A. Uehling,[84] who shows that the equations of transport are unaltered, but that the experimental coefficients require correction. These are exactly analogous to those which occur in the quantum-statistical expression for $B(T)$ (equation 4) and can be evaluated when the phases due to the relative motion of the molecules are calculated. The introduction of the quantum corrections to the calculation of the viscosity coefficients of helium, even on the rigid elastic sphere model, makes an immediate improvement in the agreement obtained on the classical theory.[84b, 85] Intercomparisons of the experimental data and rigorous calculations such as those carried out by H. S. W. Massey and R. A. Buckingham,[53] using a Slater–Kirkwood [23] potential, and E. A. Uehling and E. J. Hellund,[84c] using an in-

[77] *Physical Rev.*, 1940, **58**, 111.   [78] A. O. Nier, *ibid.*, 1939, **56**, 1009.

[79] *Idem, ibid.*, 1940, **57**, 338.   [80] H. Brown, *ibid.*, 1940, **58**, 661.

[81] *Naturwiss.*, 1938, **26**, 546; 1939, **27**, 148, 487; *Z. physikal. Chem.*, 1939, B, **44**, 397, 451.

[82] W. H. Furry, R. C. Jones, and L. Onsager, *Physical Rev.*, 1939, **55**, 1083; R. C. Jones and W. H. Furry, *ibid.*, 1940, **57**, 547.

[83] T. I. Taylor and G. Glockler, *J. Chem. Physics*, 1940, **8**, 843 (contains a complete summary of earlier references on this method). Compare also F. T. Wall and C. E. Holley, *ibid.*, p. 949; W. Krasny-Ergen, *Physical Rev.*, 1940, **58**, 1078; J. Bardeen, *ibid.*, 1939, **57**, 35; 1940, **58**, 94.

[84] (a) E. A. Uehling and G. E. Uhlenbeck, *Physical Rev.*, 1933, **43**, 552; (b) E. A. Uehling, *ibid.*, 1934, **46**, 917; (c) E. A. Uehling and E. J. Hellund, *ibid.*, 1933, **54**, 479; (d) E. J. Hellund and E. A. Uehling, *ibid.*, 1939, **56**, 818; (e) E. J. Hellund, *ibid.*, 1940, **58**, 278.

[85] H. S. W. Massey and C. B. O. Mohr, *Nature*, 1932, **130**, 276; *Proc. Roy. Soc.*, 1933, **141**, *A*, 434; 1934, **144**, *A*, 188.

ductively determined bi-reciprocal curve, in the case of helium, provide useful criteria for determining the relative accuracy of the potential curves assumed. A special consequence of the Bose–Einstein statistics, which apply to helium atoms, is that the viscosity should become appreciably pressure-dependent at 1° or 2° K., but measurements have not yet revealed this effect.[73]

Molecular Rays.—Possibly the most direct experimental approach to the measurement of intermolecular potentials is through the study of molecular rays. Technical difficulties, which have so far hindered developments in this field, are now being overcome. H. S. W. Massey and C. B. O. Mohr [85] first pointed out that, since in general the intermolecular potential will decrease more rapidly than R^{-3} at large distances, the quantum theory predicts, in contrast to the classical theory, finite cross-sections for collision which can be calculated in terms of the phases δ_l (equation 3). Thus it is possible to deduce the form of $\phi(R)$ from scattering experiments when these are carried out with sufficiently high resolution. Moreover, since the collision diameter of, *e.g.*, argon molecules moving with ordinary thermal velocities is approximately twice the internuclear distance, such data give a direct measurement of the asymptotic R^{-6} van der Waals coefficient. Values of such constants for rare-gas atoms have been calculated by H. S. W. Massey and R. A. Buckingham [86, 22] from the scattering data of S. Rosin and I. I. Rabi,[87] which are in fair agreement with values calculated in other ways. On the other hand, other investigators [88] have developed the technique of measuring the scattering of atoms moving with energies of several hundred electron-volts. Such energies may correspond to collision diameters of less than half the internuclear distance, and so provide information on the mutual repulsive potentials.   W. J. C. O.

3. ELECTRON DIFFRACTION BY GASES AND VAPOURS, AND ELECTRIC DIPOLE MOMENTS.

A Report on the theory and chemical applications of the diffraction of electrons by vapours appeared in 1936.[1] In the following year [2] a Report on the Structure and Stereochemistry of Simple Organic Molecules elaborated some of the matters discussed previously, and raised fresh ones. Since then there have been developments in the theory of the method and in its practical application which are

[86] *Nature*, 1936, **138**, 77.   [87] *Physical Rev.*, 1935, **48**, 373.

[88] I. Amdur and H. Pearlman, *J. Chem. Physics*, 1940, **8**, 7, 998; R. L. Mooney, *Physical Rev.*, 1940, **58**, 871.

[1] S. Glasstone, *Ann. Reports*, 1936, **33**, 65.

[2] L. O. Brockway and T. W. J. Taylor, *ibid.*, 1937, **34**, 196.

important because they either mark substantial advances in its actual power or indicate potentialities. There have also been many further applications of it to chemical problems.

Although there has been no general Report on the measurement and the chemical applications of electric dipole moments of molecules since 1931,[3] there have been recent Reports on special topics. In 1935 [4] there was one on the use of electric moments to determine valency angles; and in 1936 [5] one on the effect of the solvent in the measurement of moments. During the last decade there has been a vast amount of work on the theory of electric polarisability, its measurement, and its use as a tool in structural investigations or as a concept in many physicochemical, organochemical, or even biochemical problems. It is hardly an exaggeration to say that most substances which will dissolve in non-polar solvents or can be distilled safely in a water-pump vacuum have been examined; and continued efforts have been made to measure less tractable materials. It is clearly impossible to give a full account of so much work in the compass of this Report; so it is proposed to give a summary of most of the main developments in the theory of the method, and to augment this by more detailed discussions of some special topics.

Concerning the applications to chemical problems of these two experimental methods, it is important to bear in mind that neither one is so powerful and unambiguous that it alone should be relied upon when a question of molecular structure is under examination; [6] whenever possible all the methods which can be applied should be brought to bear on the problem. Although this can hardly be done thoroughly in this Report, it will be done whenever it is important to compare or contrast the conclusions from bond-length data and electric dipole-moment data. For this reason the discussion of such conclusions will be given in a separate section, tied neither to one method nor to the other.

No special attempt has been made to give complete references to the very large number of relevant papers : but those given, together with the references which they themselves contain, should constitute an adequate guide to the literature.

(i) *Electron Diffraction by Gases and Vapours.*

The Development of the Methods of Analysis.

Although an account of the methods then in use for interpreting electron-diffraction photographs was given in an earlier Report,[7] a

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[3] N. V. Sidgwick and E. J. Bowen, *Ann. Reports*, 1931, **28**, 365.
[4] S. Glasstone, *ibid.*, 1935, **32**, 126.   [5] *Idem, ibid.*, 1936, **33**, 117.
[6] L. E. Sutton, *J.*, 1940, 544.
[7] L. O. Brockway, *Rev. Mod. Physics*, 1936, **8**, 231.

brief restatement is included here as an introduction to later developments. Several reviews of the subject, including descriptions of apparatus, appeared recently,[7-13] but some of them are not readily available, and most of them are in certain respects out of date. There is need of a fresh review, more detailed than this Report can be.

When moving electrons undergo collision with other charged particles, they behave as if they have wave-character, $\lambda = h/mv$ (h = Planck's constant, m = electronic mass, v = velocity). Consequently, when large numbers of them collide with a body composed of particles which are separated by distances of the same order as λ, there is interference between the electron waves scattered by the several particles, and a diffraction pattern results which can be observed by photographic or other means. This is very similar to the diffraction which occurs when X-rays are scattered by such a body : and the photographs of X-ray or electron scattering by, e.g., gold foil are strikingly similar in qualitative character.

It has been shown * that when the diffracting agent is an assemblage of gas molecules, the following expression gives the relative intensity of scattering as a function of the angle θ between the initial beam and any direction in which we are interested (θ is known as the diffraction angle and may have any value between 0 and π) :

$$I_{\omega} = k\Sigma_i \Sigma_j \psi_i \psi_j (\sin x_{ij})/x_{ij} \quad . \quad . \quad . \quad . \quad (1)$$

k is a scale constant, and the functions ψ express the scattering powers for electrons of the several atoms, while $x_{ij} = (4\pi l_{ij} \sin \frac{1}{2}\theta)/\lambda = l_{ij}s$, λ being the electron wave-length, and l_{ij} the distance between the ith and the jth atom. If we are concerned with scattering by diatomic molecules, this expression therefore tells us that there will be scattering by the ith and jth atoms themselves, $k\psi_i^2$ and $k\psi_j^2$ respectively [since the limit of $(\sin x_{ij})/x_{ij}$ as $l_{ij} \longrightarrow 0$ is unity], with interatomic scattering expressed by $k(\psi_i\psi_j + \psi_i\psi_j)(\sin x_{ij})/x_{ij}$ superimposed on it. The intensity of the atom scattering varies with the angle only if ψ_i and ψ_j do so, whereas the occurrence in the interatomic term of the function $(\sin x_{ij})/x_{ij}$, or alternatively $[\sin (a_{ij} \sin \frac{1}{2}\theta)]/a_{ij} \sin \frac{1}{2}\theta$, means that as θ increases

[8] H. J. Emeléus and S. Miall, *Chem. and Ind.*, 1936, 952.

[9] P. Debye, *Angew. Chem.*, 1937, **50**, 3.

[10] G. B. Kistiakowsky, *J. Physical Chem.*, 1937, **41**, 175.

[11] Th. Schoon, *Angew. Chem.*, 1939, **52**, 245, 260.

[12] J. A. A. Ketelaar, *Nederland. Tijdschr. Natuurkunde*, 1938, **5**, 233.

[13] J. Y. Beach, *Pubns. Amer. Assoc. Adv. Sci.*, No. 7, " Recent Advances in Surface Chemistry and Chemical Physics," 1939, 88.

* See Refs. in Ref. (1).

from 0 to π the interatomic scattering must oscillate like a sine curve but with steadily diminishing amplitude; and so it must either augment or diminish the atomic scattering and give periodic variations in the total intensity.   The greater l_{ij} is, the more frequently will the function oscillate over a given range of θ, and conversely.   In a more complex molecule, each pair of atoms gives rise to a periodic intensity term, so the total diffraction pattern is the sum of all these and of all the atomic terms.   In addition to the scattering so far considered, termed " coherent " because the electrons undergo no change of wave-length by collision, there is " incoherent " scattering which falls rapidly as θ increases, shows no periodic character, and adds to the background.

The essential task, therefore, in the use of electron scattering for determining the interatomic distances in a molecule is to try to analyse a complex curve into its periodic components and then, knowing λ, to calculate the distances corresponding to each one.   A complete list of the distances could then be compiled.   There are two ways of attempting this.   The earlier one is the method of direct comparison, wherein several models are assumed for the molecule under examination, the theoretical curves of intensity against s [$i.e.$, $(4\pi \sin \tfrac{1}{2}\theta)/\lambda$] is calculated for them, and comparison of these with the experimental intensity curve is made.   The model giving the best-fitting theoretical curve is taken as the solution.

The later method, called the radial distribution method,[14] is based upon the idea that, strictly, a molecule should not be considered as composed of scattering points only but of scattering material spreading throughout space, though varying greatly in density. Consequently, a theoretical intensity curve should be an integral, not merely a summation; and the curve giving the radial distribution of material density is related by a process of Fourier integral inversion to the curve which expresses the intensity of scattering as a function of scattering angle.   Just as the former can be used to calculate the latter if a molecular model be assumed, so the former should be calculable from the latter, experimental curve.   The approximation which is made when a model is assumed, $viz.$, that scattering is only from points, is very good; but the corresponding assumption which was at first made in calculating the radial distribution curve from the scattering curve, $viz.$, that the interatomic scattering is discontinuous, and gives only sharp maxima or minima, is not so good; and it constitutes a considerable drawback to the application of the method.   Nevertheless, as will be shown later, the method has been very useful.

Before any relation of the distribution of matter with the way in

[14] L. Pauling and L. O. Brockway, $J. Amer. Chem. Soc.$, 1935, 57, 2684.

which it scatters electrons can be attempted, we must know some-
thing about its ability to scatter, *i.e.*, about the scattering functions
ψ for the atoms concerned.   For fast electrons accelerated by a
potential of 30 kv. or more, it may be shown that for any atom i

$$\psi_i = (Z_i - f_i) \Big/ \Big(\frac{\sin \frac{1}{2}\theta}{\lambda}\Big)^2,$$

where Z_i is the atomic number of i, and f_i is its ability to scatter
X-rays (θ and λ have their earlier meanings).   Now X-rays are
scattered because the electric component of the wave induces
vibrations in the electronic clouds round the atoms, but the wavelets
scattered from different parts of the diffuse cloud round any atom
may interfere destructively and this happens increasingly as θ
increases; f_i itself varies with θ, increasing as θ decreases, and when
$\theta = 0$ it equals Z_i.   The meaning of the electron-scattering factors
is therefore that the screening of the nuclei by the electronic clouds
round them is less the greater θ is, *i.e.*, that the scattering at low
values of θ is predominantly by the electrons whereas at large values
it is predominantly by the nuclei.[15]   Although $Z_i - f_i$ increases as
θ increases, the denominator $[(\sin \frac{1}{2}\theta)/\lambda]^2$ increases so much faster
that ψ_i falls very rapidly.   So rapid is the fall in the atomic back-
ground and in the interatomic factors that the maxima and minima
in the periodic functions on which the factors operate are reduced to
mere inflexions on a rapidly falling curve, except at small values
of $(\sin \frac{1}{2}\theta)/\lambda$.   Moreover, unless the relative importance of the
interatomic terms to the atomic ones is rather large, these inflexions
are shallow; and in a microphotometer record of a diffraction photo-
graph they are further obscured by the zigzag caused by emulsion
grain.   Although this last difficulty can be mitigated by rotating
the plate about the central spot when taking the microphotometric
record,[16] it is difficult to correlate more than five inflexions with the
theoretical curve, and furthermore, the calculation of the latter is
extremely tedious unless the molecule is very simple.   Although a
few substances have been examined in this elaborate manner,[15, 17]
the rapid application of the method to large numbers of compounds,
many of them quite complex, would have been impossible unless
simpler approximate methods had been developed.

The earliest and most drastic of these has proved, with but little
modification, to be the most satisfactory.   Although the blackening
of a diffraction photograph diminishes steadily from the central spot
outwards, by a singularly impressive optical illusion the human eye

[15] M. H. Pirenne, *J. Chem. Physics*, 1939, **7**, 144.
[16] C. Degard, J. Piérard, and W. van der Grinten, *Nature*, 1935, **136**, 142
[17] L. Pauling and L. O. Brockway, *J. Chem. Physics*, 1934, **2**, 867.

sees dark and light rings superimposed on a slowly falling background, and these do not diminish in intensity nearly so rapidly as would be expected from the full theoretical curve. Roughly speaking, the eye appears to subtract the background and divide by it. Now if this be done literally in the proper expression for the intensity,[17] we obtain

$$\text{physiol.} I_{\text{co.}} = k' \frac{\Sigma_i \Sigma_j' \psi_{ij} \dfrac{\sin x_{ij}}{x_{ij}}}{\Sigma_i \psi_i^2} = \frac{\Sigma_i \Sigma_j' (Z_i - f_i)(Z_j - f_j) \dfrac{\sin x_{ij}}{x_{ij}}}{\Sigma_i (Z_i - f_i)^2},$$

If further we assume that f is the same function of θ for all atoms concerned, say $ZF(\theta)$, we obtain by cancellation of $[1 - F(\theta)]^2$,

$$\text{physiol.} I_{\text{co.}} \sim k'' \Sigma_i \Sigma_j' Z_i Z_j (\sin x_{ij})/x_{ij}. \quad . \quad . \quad . \quad (2)$$

k'' being a scale constant.

Empirical tests have, in fact, shown that this expression reproduces with surprising accuracy what the eye observes. Where this curve shows maxima, minima, double maxima, or shelves, the eye sees them. Consequently, by observing visually the values of $(\sin \tfrac{1}{2}\theta)/\lambda$ at which maxima or minima occur, and then comparing them with those read off from the graph of expression (2) as a function of $(\sin \tfrac{1}{2}\theta)/\lambda$ or $(4\pi \sin \tfrac{1}{2}\theta)/\lambda$, one of the two steps necessary in correlating the experimental and the theoretical curve is achieved. The other step is the comparison of the observed and the calculated intensities of the several maxima and minima. This cannot be done nearly so satisfactorily by eye especially if, as with the older cameras, there is, in addition to the coherent atomic scattering and the incoherent scattering, an " experimental " background caused by accidental X-rays, or by scattering occurring outside one very small volume element near the vapour jet owing to inadequate pumping and condensation. If a maximum appears denser than one immediately inside, it can be safely concluded that this feature should appear on the theoretical curve, but if the outer maximum appears the fainter, then this does not necessarily mean that the theoretical maxima must bear this relation, for the eye is conscious of some fall in background. Estimates of relative intensity are equally necessary whether the method of analysis is that of direct comparison or radial distribution, and in view of the limitations of the human eye as an instrument for this purpose it is fortunate that, as a rule, intensity is less important than position.

It is obviously desirable both in principle and in practice to develop a method for observing diffraction which is objective and is simple to apply. Clearly, what is wanted is a means of obtaining an experimental intensity curve which can be correlated with the convenient, simple theoretical intensity curve given by expression

(2) ; a means, in fact, of actually subtracting the background and of dividing by it, so as to show the intensity of the fluctuations relative to the background. Attempts to approximate to this were made by various methods ; by making a microphotometer record with a graded positive, designed to compensate for the background, placed over the electron-diffraction negative,[18] or by using a rotating sector in place of the positive.[19] The use of a differential photometer has also been explored.[20] All these methods have one common disadvantage, however, in that they employ the usual diffraction photograph as a basis. The range of intensity of scattering within the range of θ which is important is, however, very great, and commonly exceeds the limits of linear response of the photographic emulsion. Attempts have therefore been made to photograph the electron scattering itself through a compensating sector.[21, 22] This necessitates having rotating mechanism in a high-vacuum chamber, which raises technical problems, but the results so far published appear very promising, for several real maxima and minima have been obtained on a microphotometer record even for hydrides such as ammonia and acetylene. If this method can be satisfactorily developed it offers a prospect of more accurate and detailed analysis than has yet been possible without very great trouble, and also of power to determine the structure of lighter molecules than could formerly be dealt with. It would also justify the use of a rather more accurate expression for the scattering intensity than (2). It will be remembered that in the latter the assumption was made that the X-ray scattering factor f is the same function $ZF(\theta)$ of the scattering angle for all atoms in the molecule. Although this is a good approximation if the atoms are all in the same period, it is far from satisfactory if they come from widely separated periods, and the difference can affect the relative intensities,[15] or even to some extent the positions, of theoretical maxima and minima for any but diatomic molecules. Correction for this has been made in some of the most recent determinations,[23] but probably it is hardly necessary until the shape of the experimental curve can be measured more satisfactorily. If this can be done, then, since the actual electron-scattering factors for the lighter elements decrease proportionately less rapidly with increasing θ than

[18] V. E. Cosslett, *Trans. Faraday Soc.*, 1934, **30**, 981.

[19] F. Trendelenburg, *Naturwiss.*, 1933, **21**, 173; F. Trendelenburg and H. Franz, *Veröff. Siemens-Konz.*, 1934, **13**, 48; F. Trendelenburg, *Physikal. Z.*, 1939, **40**, 727.

[20] F. W. Sears, *J. Opt. Soc. Amer.*, 1935, **25**, 162.

[21] H. Mark, private communication.

[22] P. Debye, *Physikal. Z.*, 1939, **40**, 66, 404, 507.

[23] D. P. Stevenson and V. Schomaker, *J. Amer. Chem. Soc.*, 1940, **62**, 1913.

do those for the heavier elements, it should be possible to determine
the positions of the former in a molecule more easily than would be
expected if the atomic numbers are taken to be the scattering
factors as in expression (2).   Conversely, X-ray diffraction should
emphasise the contributions of the heavier atoms, and consequently
the two methods should be complementary.   In principle, it is
even possible to determine the distribution of electrons within
a molecule by studying the electron diffraction at small angles,
when electron screening is very marked (p. 40).[15]   Realisation
of these theoretical possibilities depends, however, upon technical
developments.

A further complication in analysis, which is proving to be of some
practical importance, is the effect of thermal vibration on the diffrac-
tion pattern.   It has been shown [7, 24] that if two atoms, i and j, are
vibrating with a mean square amplitude $(\delta l_{ij}^2)_{Av}$ their scattering is
expressed by

$$I = ke^{-A_{ij}}\psi_i\psi_j(\sin x_{ij})/x_{ij}$$

where $A_{ij} = 8\pi^2(\delta l_{ij}^2)_{Av}[(\sin \frac{1}{2}\theta)/\lambda]^2$, and ψ_i and x_{ij} have their
previous meaning.   The effect of the exponential term is to decrease
the amplitude of the intensity fluctuations, and this effect is more
marked the greater $(\delta l_{ij}^2)_{Av}$ is, as might be expected, and the
greater θ is.

Consequently, it becomes essential to allow for this temperature
effect when trying to match a theoretical curve to observed intensi-
ties if θ is large [for most molecules it is necessary if $s = (4\pi \sin \frac{1}{2}\theta)/\lambda$
> 15] or if certain distances may be considerably affected by
vibration even at low temperatures, $i.e.$, if vibrational force constants
are low.   It has been observed that the pattern for the stannous or
plumbous iodides shows practically no effect of the I–I diffraction
term, and this is attributed to a large temperature effect arising
from the relative ease with which a valency angle can bend.[25]
Terms which are affected by " free rotation " are likely to be greatly
diminished.[23]   For a complex molecule, wherein it is possible that
the force constants may vary greatly, the periodic terms for different
pairs of atoms will therefore vanish in order as θ increases, the
" soft " distances going first and the " hard " ones last.   This may
help in the analysis of the pattern, for it may make possible some
separation of parameters; the " hard " distances being determined
first, from the outer rings, and then taken as known in order that
the " soft " distances may be derived from the inner rings.   The
general considerations underlying present and potential methods of

[24] R. W. James, *Physikal. Z.*, 1932, **33**, 737.
[25] Work by Dr. M. W. Lister at Oxford, shortly to be published.

analysis having been presented, it remains to say something about their detailed application, and to assess their reliability.

The radial distribution method is, in principle, a much neater way of making use of the same data, *viz.*, the positions and the relative intensities of maxima and minima, than the method of direct comparison; but it is every whit as empirical in the form used,[26] and moreover, since it uses the same experimental data it can give no more information though it may give it more easily. In the original form of the method the visual intensity curve was used, and there was no attempt to take into account its full shape as was required by the integral form of the radial distribution expression

$$\mathrm{D}(r) = k'' \int_0^\infty s^6 I(s)[(\sin sr)/sr]\mathrm{d}s,$$

Instead it was assumed to consist only of instantaneous maxima and minima, *i.e.*, a summation of a few terms was used instead of an integral in order to make the method practicable. This procedure, as judged by the other more certain though more pedestrian method, was not very satisfactory, for it gave poor resolution of distances and unreliable values. A simple explanation of this was that it gave too much importance to the early, intense maxima which were known to be difficult to place accurately. More detailed theoretical considerations indicated the desirability of multiplying the visual intensities by an exponential weight factor $s_k^2 e^{-as_k^2}$, s_k being the position of the kth maximum, and a being chosen so that the ratio of the weighted intensities of the strongest and the weakest maximum is as $10 : 1$.[27] * This increases the relative importance of the outer maxima, and is found to give improved resolution. More recently an attempt has been made to take into account more fully the shape of the curve by considering maxima and minima, not as lines, but as segments of cosine curves.[28] This treatment leads to a more elaborate but quite convenient approximate expression which is

[26] For discussion of the validity of the treatment, see P. Debye and M. H. Pirenne, *Ann. Physik*, 1938, **33**, 617; P. Debye, *Physikal. Z.*, 1939, **40**, 573; and (27).

[27] C. Degard, *Bull. Soc. chim. Belg.*, 1938, **47**, 770.

[28] J. Walter and J. Y. Beach, *J. Chem. Physics*, 1940, **8**, 601.

* (Added in proof, 18/2/41.) This procedure is the one followed at Oxford in accordance with the tradition brought over by Dr. L. O. Brockway in 1937. It appears not to be the same as that which is indicated in the paper by J. Walter and J. Y. Beach [28] and which is said to be the common practice at Pasadena and at Princeton. The report of the A.C.S. meeting at Baltimore in 1939, to which American authors sometimes refer, gives no exact account of the procedure. It could be wished that a full description might be published in a readily accessible journal.

found to give still better resolution and placing of the peaks of the $r^2D(r)$–r curve when applied to some theoretical intensity curves and compared with the older procedures. The radial distribution method in one form or another is very useful for a preliminary analysis, for it makes possible the elimination of certain models and gives a useful guide to those which should be investigated by trial and error. Direct comparison of theoretical intensity curves with the visual appearance of the photographs must, however, still be regarded as the more tried and trusted method; and it is still necessary for settling the final model and for establishing the limits of accuracy in determination of the several parameters.

The use of a set of $(\sin ax)/ax$ strips [29] in conjunction with an electric calculating machine, or of sets of punched cards in a machine of the International Business Machine or Hollerith type, brings the labour of computation within reasonable limits.

The subjective nature of the most-used methods of interpretation of electron-diffraction photographs has caused the results to be received with some scepticism by exponents of other methods of measuring interatomic distances; but experience has shown that it can be as accurate as any. The factors which decide [7] are the number of important, independent parameters in the molecule,* the relative importance of the interatomic and the atomic scattering terms,† the physical characteristics of the material—for very volatile substances, being less easy to condense, give less clear photographs, whereas non-volatile ones may show large temperature effects when vaporised—and the accuracy with which voltage (for determining λ) and distances in the camera and on the plates can be measured.

The tests of the method are of two kinds, *viz.*, direct, by comparing results obtained for the same molecule or the same bond by electron-diffraction and by other methods; and indirect, by comparing values obtained for interatomic distances with those predicted for them from atomic covalent radii which were derived through other methods. Some comparisons of the first type are given in the following table which, though not exhaustive, should suffice to show that the agreement is on the average within 1 % and that the discrepancies are not noticeably systematic.

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[29] Originally published by Prof. P. C. Cross of Brown University, Providence, Rhode Island, U.S.A.

* The importance of the parameter l_{ij} is determined by the magnitude of $n\psi_i\psi_j$ compared with the corresponding products for other interatomic distances, where n is the number of occurrences of l_{ij}.

† The factor determining the clarity of the rings in a diatomic molecule is $2(\psi_i\psi_j)/(\psi_i^2 + \psi_j^2)$, which has a maximum value when $\psi_i = \psi_j$.

Bond.	Electron diffraction.			Other method.			Diff., %.
	Substance.	Value, Å.		Substance.	Value.	Method.*	
Cl–Cl	Cl_2	2·009 [17]		Cl_2	1·984 [17]	Sp.	+1·2
Br–Br	Br_2	2·289 [17]		Br_2	2·281 [17]	Sp.	+0·35
I–I	I_2	2·64 [17]		I_2	2·66 [17]	Sp.	−0·75
I–Cl	ICl	2·30 [17]		ICl	2·315 [17]	Sp.	−0·65
S–S	S_2(v)	2·1 [30]		S_2(c)	2·10 [31]	X-Ray	—
				S_2(l)	2·08 [32]	X-Ray	—
P–P	P_4(v)	2·21 [32]		P_4(l)	2·25 [34]	X-Ray	−1·8
As–As	As_4(v)	2·44 [32]		As_4(c)	2·50 [35]	X-Ray	−2·5
C–C	C_nH_{2n+2}	1·52—1·55 [36]		Diamond	1·54 [35]	X-Ray	—
Ge–Ge	Ge_nH_{2n+2}	2·41 [37]		Ge(c)	2·44 [35]	X-Ray	−1·25
C–C	C_2H_4	1·34 [36]		C_2H_4	1·33 [38]	Sp.	+0·75
	$CH_3·C:CH_3$	1·34 [36]		$CH_3·C:CH_3$	1·33 [39]	Sp.	+0·75
$C_{al}.–C_{ac}.$	$CH_3·C:CH$	1·46 [40]		$CH_3·C:CH$	1·462 [41]	Sp.	−0·1
$C_{al}.–C_{ar}.$	$C_6(CH_3)_6$(v)	1·54 [36]		$C_6(CH_3)_6$(c)	1·53 [43]	X-Ray	+0·65
$C_{ar}.–C_{ar}.$	$C_6(CH_3)_6$(v)	1·39 [36]		$C_6(CH_3)_6$(c)	1·39 [43]	X-Ray	0·0
CCl	CCl_4(v)	1·75 [16, 17]		CCl_4(v)	1·75 [16]	X-Ray	0·0
Si–Cl	$SiHCl_3$(v)	2·01 [43]		$SiHCl_3$(v)	1·98 [15]	X-Ray	+1·5

* Sp. = spectroscopic, (c) = crystalline, (l) = liquid, (v) = vapour.

Under the second heading come many measurements; especially those of bonds between sulphur atoms in H_2S_2 and $(CH_3)_2S_2$,[44] between possible pairs in carbon, nitrogen, and oxygen, and between carbon and most of the elements with which it forms covalent bonds.[35] The agreement, usually to within 1%, between so many such values and the corresponding series of the atomic covalent radii which were mostly derived from spectroscopic or X-ray measurements may be considered to show both that the radii are accurate and that the electron diffraction method is reliable within the limit given.

There are, it is true, some larger discrepancies to which attention has been directed, especially for the carbon–halogen bonds in methyl fluoride and chloride for which the electron-diffraction values are 1·42 and 1·77 A. as against 1·385 and 1·66 A. by spectrum analysis;[45] i.e., they are 2·5% and 6·6% greater than the latter. This disagreement has not yet been resolved,[2] but it is perhaps significant that later spectroscopic work may be interpreted as giving

[30] L. R. Maxwell and V. M. Mosley, *Physical Rev.*, 1936, **49**, 199.

[31] B. E. Warren and J. T. Burwell, *J. Chem. Physics*, 1935, **3**, 6.

[32] N. S. Gingrich, *ibid.*, 1940, **8**, 29.

[33] L. R. Maxwell, V. M. Mosley, and S. B. Hendricks, *ibid.*, 1935, **3**, 698.

[34] C. D. Thomas and N. S. Gingrich, *ibid.*, 1938, **6**, 659.

[35] L. Pauling, "The Nature of the Covalent Bond," Cornell, 1939, Chap. V.

[36] L. Pauling and L. O. Brockway, *J. Amer. Chem. Soc.*, 1937, **59**, 1223.

[37] L. Pauling, A. W. Laubengayer, and J. L. Hoard, *ibid.*, 1938, **60**, 1605.

[38] W. L. Penney, *Proc. Roy. Soc.*, 1937, A, **158**, 306.

[39] E. H. Eyster, *J. Chem. Physics*, 1938, **6**, 580.

[40] L. Pauling, H. D. Springall, and K. J. Palmer, *J. Amer. Chem. Soc.*, 1939, **61**, 927.

[41] G. Herzberg, F. Patat, and H. Verleger, *J. Physical Chem.*, 1937, **41**, 123; R. M. Badger and S. H. Bauer, *J. Chem. Physics*, 1937, **5**, 599.

[42] L. O. Brockway and J. M. Robertson, *J.*, 1939, 1342.

[43] L. O. Brockway and J. Y. Beach, *J. Amer. Chem. Soc.*, 1938, **60**, 1836.

[44] D. P. Stevenson and J. Y. Beach, *ibid.*, p. 2872.

[45] G. B. B. M. Sutherland, *Trans. Faraday Soc.*, 1938, **34**, 325.

a value of 1·71 A. for C–Cl in methyl chloride,[46] which reduces the discrepancy to 3·6%.

The investigations of bond lengths in elements could not be affected by possible error due to ignoring the different rates of variation of the X-ray scattering factor, f, with θ for different elements, but the second class of investigations might be, for it consists of measurements on compounds, and these were nearly all made without any correction. The fact that they show as good agreement as the results in the first class indicates that the effect is not serious.

This method of investigating the distribution of matter in a molecule is clearly a very potent one already; and it will steadily become more effective. We may hope, not only that it will give detailed information about small molecules, but that useful approximate methods of analysing the scattering by large, complex molecules will be developed, so that a limited but useful amount of information can be derived from them. A step in this direction has been taken in the examination of pp'-di-iododiphenyl ether for the purpose of measuring the I–O–I angle;[33] when instead of taking, as is usually done, the length of an arbitrary bond, or an Ångström unit, as the unit of length in which all the coefficients of s in the $(Z_iZ_j \sin l_{ij}s)/l_{ij}s$ terms are expressed, the distance between iodine atoms was chosen as the unit in any particular model. Obviously, if the scattering were due only to the two iodine atoms, the maxima and minima in the graph of theoretical intensity against s would then come at the same s values, whatever the value of the I–O–I angle, for the curve is only a function of this angle if the latter comes into the expression for l_{II} in whatever units are chosen : and if l_{II} itself is the unit it does not. Hence, if the intensity curves for a series of models be so plotted, maxima due primarily to I–I scattering will remain stationary but others will not. In this way the former can be detected, and the iodine–iodine distance can be calculated.

It is possible, also, that the rotating-sector device could be used to compensate for the scattering of all the terms save one, such as an iodine–iodine term, so that this alone would be photographed and used to determine one distance of particular interest.

(ii) *Electric Dipole Moments.*

Developments in Methods of Determination and in the Theory of Polarisation.

In the last ten years there has been no startling development in experimental methods of measuring electric dipole moments; and

[46] G. B. B. M. Sutherland, *J. Chem. Physics*, 1939, **7**, 1066.

as yet there has been no quantitative determination of the quadripole moment of a molecule, although qualitative indications of such moments have been observed.[47] By far the most important still are the early methods based on the study of the variation with temperature of the electric polarisability of a molecule, or on its variation with the frequency of the applied field as in the common method of measuring it at medium radio frequencies, through the dielectric constant, and at visible frequencies, through the refractive index.[48] There have been improvements in details of apparatus and experimental technique, especially in the design of constant-frequency oscillators.[49] Greater emphasis has been placed on measurements in the vapour phase owing to the difficulties now known to be inherent in measurements made in solution (see p. 51). The " beam " method, in which the dispersion of a beam of molecules by an inhomogeneous field is studied, has been developed [50] but is still far from being readily or generally applicable.

The early quantitative theory thereof was developed for diatomic molecules, and made possible determinations of moments of some ion-pairs which could not be attempted by any other means.[51] Recently, the theory for more complex molecules with the moment parallel to a possible axis of rotation has been developed; [52] and it has been shown that the dispersion of these ought to depend upon the first power of the field strength, as well as upon the square as for molecules with moments perpendicular to possible axes of rotation. Experimental application of the theory to ammonia [53] showed the existence of this linear effect but gave a value of 0·5 D. for the moment, which is only one-third of that (1·46 D.) given by other methods. The reason for this discrepancy is not yet clear.

There was one development which may become of considerable

[47] F. H. Müller, *Wiss. Veröff. Siemens-Werken*, 1938, **17**, No. 1, p. 20.

[48] (a) P. Debye, " Polar Molecules," New York, 1929; (b) C. P. Smyth, "Dielectric Constant and Molecular Structure," New York, 1931; (c) P. Debye, *Trans. Faraday Soc.*, 1934, **30**, 679; (d) H. A. Stuart, " Molekül-struktur," Berlin, 1934; (e) O. Fuchs and K. L. Wolf, " Dielektrische Polaris-ation," " Hand- und Jahrbuch der chemischen Physik," Band 6, I, Leipzig, 1935; (f) R. J. W. LeFèvre, " Dipole Moments," London, 1938.

[49] (a) J. D. Stranathan, *Rev. Sci. Instr.*, 1934, **5**, 334; 1938, **6**, 395; (b) L. G. Groves and S. Sugden, *J.*, 1934, 1094; (c) I. E. Coop and L. E. Sutton, *J.*, 1938, 1269; (d) L. G. Groves, *J.*, 1939, 1144; also 48 (f) and a forthcoming paper by G. I. M. Bloom and L. E. Sutton.

[50] (a) R. Fraser, " Molecular Rays," Cambridge, 1931; (b) I. Estermann and R. G. J. Fraser, *J. Chem. Physics*, 1933, **1**, 390.

[51] (a) H. Scheffers, *Physikal. Z.*, 1934, **35**, 425; (b) W. H. Rodebush, L. A. Murray, and M. E. Bixler, *J. Chem. Physics*, 1936, **4**, 372; (c) R. G. J. Fraser and J. V. Hughes, *ibid.*, p. 730.

[52] H. Scheffers, *Physikal. Z.*, 1940, **41**, 89.

[53] *Idem, ibid.*, p. 98.

importance.   It has long been known that in principle it is possible
to derive values of the electric dipole moment of a diatomic molecule
from the absorption coefficients for its pure rotation lines in the far
infra-red, or of a single bond in a symmetrical molecule, such as the
C–H bond in methane, if the absorption coefficient of the lines
corresponding to its optically " active " bending frequencies can be
determined.   The requisite measurements are extremely difficult,
but a rather easier alternative is to study the variations of the
refractive index in the region of the spectral lines.[54]   The most
recent investigations of the latter kind have given a value of 1·18 D.
for the moment of hydrogen chloride,[55] which agrees quite well with
the most recent value of 1·085 D. from the polarisation of the
vapour,[56] and of 0·307 D. for the moment of the C–H bond.[57]   An
estimate of the latter value has also been made, on the basis of a
less exact theoretical treatment, from measurements of absorption
coefficients for rotation–vibration overtones in chloroform, and is
in good agreement with the above value, being 0·3—0·4 D.[58]   A
theoretical calculation by the molecular orbital method has given
0·53 D., but this method is likely to yield a high value.[59]   The
importance of such a determination of one single bond-moment in a
complex molecule is that it makes possible the evaluation of the
moments of the other bonds : otherwise, only differences relative to,
say, the C–H bond are known.

The theory of the polarisability (commonly called polarisation)
methods has been considerably developed in the period under
review.   There are two parts to the problem.   The first consists of
finding how a polar molecule will behave in an applied uniform
electric field of known strength ; the second consists of finding how
the strength of the field acting on a molecule in a mass of dielectric
material is related to that of the applied external field.   The first
question has been answered with a great deal of certainty by the
application of quantum mechanics.[48a, 54]   It is satisfactory to find
that, except at low temperatures, the result obtained initially by a
simple classical treatment is valid.   The predicted divergence from
the classical curve is just detectable in the case of hydrogen and
deuterium chlorides.[56]   The second question is more complex and
is less susceptible of precise treatment.   The original treatment by
Clausius and Mosotti involved the assumption that the field in

[54] J. H. Van Vleck, " The Theory of Electric and Magnetic Susceptibilities,"
Oxford, 1932.

[55] R. Rollefson and A. H. Rollefson, *Physical Rev.*, 1935, **48**, 779.

[56] R. P. Bell and I. E. Coop, *Trans. Faraday Soc.*, 1938, **34**, 1209.

[57] R. Rollefson and R. Havens, *Physical Rev.*, 1940, **57**, 710.

[58] B. Trimm and R. Mecke, *Z. Physik*, 1935, **98**, 363.

[59] C. A. Coulson, *Proc. Camb. Phil. Soc.*, 1940, **36**, 509.

question could be made up of three parts : (1) the primary field, (2) the field from the charges on the outside surface of the dielectric mass and on the inside of a spherical cavity centred about the test molecule, (3) that from the substance inside the cavity. In the simple treatments, the third force was assumed to be zero. Furthermore, the dipole molecule was assumed to have no action upon the surrounding medium, and therefore this effect could have no reaction upon the dipole even if it were polarisable. In the ideal case of a dilute gas these assumptions are perfectly adequate; but as the density of the material increases they become increasingly invalid, and the departures from the simple theory are commonly ascribed to dipole–dipole interaction or association. If the dielectric material is a solution, there is also dipole–solvent interaction.

In order to take account of these effects a number of treatments have been proposed which have had some measure of success. No detailed account of them will be given here. Early developments were fully reported in 1936,[5] and recent developments, the most important of which are concerned with applying and developing L. Onsager's treatment,[60] have not come very much nearer to solving the practical problem, although they have helped greatly to elucidate the character of intermolecular forces.[61] The general nature of the problem is now clear and it is obviously difficult to solve exactly. The forces between molecules at short distances depend upon several factors including some which are difficult to express simply, such as "shape," and the spatial distribution of positive and negative charges; or which are difficult to determine with sufficient accuracy, such as "nearest distance of approach" or partial "saturation effects" when molecular orientation occurs in local fields. These difficulties can be overcome to some extent by introducing con- venient experimental parameters such as the Kerr constant, but not usually with complete quantitative success. Progress has become semi-empirical. It was once hoped to find a solution of the problem which would make it possible to measure the polarisation of a polar

[60] J. Amer. Chem. Soc., 1936, 58, 1486.

[61] See (a) W. H. Rodebush and C. R. Eddy, J. Chem. Physics, 1940, 8, 424; (b) J. Norton Wilson, Chem. Reviews, 1939, 25, 377; (c) A. Piekara, Proc. Roy. Soc., 1939, A, 172, 360; (d) J. G. Kirkwood, J. Chem. Physics, 1939, 7, 911; (e) C. P. Smyth, J. Physical Chem., 1939, 43, 131; (f) M. E. Hobbs, J. Chem. Physics, 1939, 7, 849; (g) C. J. F. Böttcher, Physica, 1939, 6, 59; (h) A. H. White, J. Chem. Physics, 1939, 7, 758; (i) R. H. Cole, ibid., 1938, 6, 385; (j) K. L. Wolf, H. Frahm, and H. Harms, Z. physikal. Chem., 1937, B, 36, 237; (k) F. H. Müller, Physikal. Z., 1937, 38, 498; (l) P. Debye, Physikal. Z., 1935, 36, 100, 193; (m) F. R. Goss, J., 1940, 1752; (n) E. G. Cowley and J. R. Partington, J., 1938, 1598; (o) G. Thomson, J., 1938, 460; K. Higasi, Sci. Papers Inst. Phys. Chem. Res. Tokyo, 1937, 31, 311; and further references therein.

solute in any chosen solvent at any arbitrary concentration (or even to use a pure polar liquid) and then, by introducing experimental parameters of solvent and solute which could readily be measured, to calculate accurately the moment of a free molecule such as would be obtained from the polarisation of a dilute gas.   This goal has not yet been achieved and it is now clear that in general no simple method can be perfect, nor perfect method simple; but if the solvent be non-polar, the solution infinitely dilute, and if, further, the solute be similar in shape to one for which there are sufficiently extensive data, a reasonably satisfactory answer can usually be obtained.

The lack of a satisfactory theoretical basis for treating solutions in polar solvents is felt particularly in the investigation of large and highly polar molecules, especially those of biological interest such as peptides and proteins which can only be examined in aqueous solution.   An empirical relation between solute polarisation and dielectric increment has been developed from studies of solutions of the amino-acids, for which the moment can be estimated, if certain assumptions about the structure be granted, or derived from other experimental data.[62]   When this relation is applied to protein solutions, it gives values of several hundred Debye units for the moments of the proteins.   These results are discussed later (p. 56).

Certain unusual solute–solvent interactions have been discovered. The moments of the hydrogen halides are greater in solution than in the vapour phase, possibly because the importance of the ionic structure is raised by the increased dielectric constant of the medium.[63]   Donor molecules and certain polar hydrogen compounds, such as chloroform, form what appear to be weak hydrogen bonds.[64]

Another matter in which there has recently been considerable clarification of ideas is that of the effect of intramolecular vibrations upon the electric polarisability.   There appear to be two possible cases to consider, according to whether the non-vibrating molecule is polar or not.   In the former case the effect of vibration is likely to be of minor importance, but in the latter it may be major.   The subject is sufficiently important and timely to warrant a separate, detailed discussion in a later section; and here only a brief recital of conclusions and results will be given.   It would be expected that in hydrogen-containing polar molecules such as water or ammonia,

[62] J. Wyman, *Chem. Reviews*, 1936, **19**, 213; S. Arrhenius, *Physikal. Z.*, 1939, **40**, 534.

[63] F. Fairbrother, *Trans. Faraday Soc.*, 1937, **33**, 1507.

[64] (*a*) S. Glasstone, *ibid.*, p. 200; (*b*) D. Ll. Hammick, A. Norris, and L. E. Sutton, *J.*, 1938, 1755.

in which the valencies may be executing anharmonic vibrations relative to each other, the substitution of deuterium for protium would, through decreasing the amplitude of vibration, reduce the mean intervalency angle and hence increase the moment.   Such a difference has been observed between light and heavy ammonia,[65] but in water the smaller predicted difference has not been detected. A related isotope effect is to be expected in vibrating diatomic molecules, for in hydrogen chloride the interatomic distance should be greater than in deuterium chloride, and the moment should be changed by $\Delta r \cdot d\mu/dr$.   Now, dispersion measurements in the infra-red give values of $(d\mu/dr)^2$, but do not give $d\mu/dr$; so although the magnitude of the difference can be predicted the sign cannot be obtained from these data alone.   If the bond is essentially covalent, then when it is stretched indefinitely the molecule dissociates into two neutral atoms, which form a non-polar system, and conversely, if the internuclear separation is diminished to zero, another non-polar system is obtained.   Between these two limits the system must be polar, so there must be a distance for which the moment is a maximum ; but it is impossible to predict whether this will be greater or less than the equilibrium distance, and therefore whether $d\mu/dr$ is positive or negative.   The numerical agreement of the theoretical and experimental differences for hydrogen chloride and deuterium chloride is as good as can be expected, and furthermore the algebraic difference leads to the interesting conclusion that $d\mu/dr$ is negative.[66]   On the modified ion-pair model of the molecules with a partial electronic charge on each atom it should obviously be positive ; and consequently the failure of this prediction shows that so simple a model is far from adequate.*

Consideration of the effect of vibration in non-polar molecules suggests that there are two possible effects : one is that the field bends the symmetrical molecule and induces a " distortion " moment ; the other that the molecule bends under thermal impact and orients as a polar molecule while still bent.   The latter is the physical

[65] J. M. A. De Bruyne and C. P. Smyth, *J. Amer. Chem. Soc.*, 1935, **57**, 1203.

[66] R. P. Bell and I. E. Coop, *Trans. Faraday Soc.*, 1938, **34**, 1209.

* (Added in proof, 18/2/41.)   It has been pointed out by Prof. M. Polanyi, in a discussion, that either the relative positions given for the minima of the potential energy curves for H–Cl and H^+Cl^- (see Pauling, ref. 35, p. 43, or *J. Amer. Chem. Soc.*, 1932, **54**, 988) or the fact that the sum of the ionic radii $(0 + 1\cdot81 = 1\cdot81$ A.) is greater than the normal interatomic distance $(1\cdot28$ A.) should mean that the ionic character increases when the ordinary HCl bond is slightly extended.   The observed negative value of $d\mu/dr$ is not in agreement even with this more sophisticated molecular model, and is therefore of great interest.

picture which has usually been employed as a basis for treatments of the effect of " free rotation " in such molecules as ethylene dichloride. More careful consideration shows that the two processes are statistically indistinguishable, and it may therefore be best that what were called " atom polarisation " and the " polar character of flexible molecules " should both be called " vibration " polarisation. Provided that the vibration be harmonic and of small amplitude, the resulting polarisation is likely to be independent of temperature. There is little doubt now that most of the anomalous polarisations of molecules which should on the usual structural principles be non-polar, are really large vibration polarisations, and are not due to a solvent effect as was once suggested (Section iii).

It had long been realised that the difficulty of measuring the atom polarisation in polar molecules was a bar to the accurate determination of electric moments. If the polarisation of the vapour of the substance can be studied over a sufficient range of temperature, usually $100°$, this difficulty can be overcome, but otherwise it is necessary to make an empirical allowance for P_A as 5—15% of P_E,[67, 68] or to study the infra-red dispersion. A number of direct measurements of vibration polarisation have recently been carried out thus, by following the changes of refractive index of liquids, or of solutions, in passing from the visible frequencies through the infra-red region until the effect of orientation absorption becomes manifest.[69] They have provided several instances where the values for the atom or vibration polarisation P_A are somewhat different when measured in this way and by determination of the sum of the atom and the electron polarisation from the curve of P plotted against $1/T$. It is suggested that the error is probably in the dielectric measurements.

One factor which has frequently complicated the interpretation of dipole-moment data is the relatively large moments which a polar bond or group may induce in other parts of a molecule. Such was presumed to be the reason for the increase in moment with chain length in homologous series, the incorrectly large values calculated for the angles between polar valencies, and part of the differences between the moments of aromatic and aliphatic compounds.[48b, 48e, 70, 71] In general, it is necessary to allow for these induction effects in quantitative stereochemical applications, and

[67] See ref. 48 (e), p. 299.
[68] L. G. Groves and S. Sugden, J., 1937, 1779.
[69] C. H. Cartwright and J. Errera, Proc. Roy. Soc., 1936, A, **154**, 138; also refs. 54, 55, 57.
[70] H. M. Smallwood and K. F. Herzfeld, J. Amer. Chem. Soc., 1930, **52**, 1919.
[71] L. E. Sutton, Proc. Roy. Soc., 1931, A, **133**, 668.

in attempts to calculate individual bond moments, or to detect "abnormalities" in moments of a whole molecule.

The difficulty of accurately so doing has been a great nuisance. Several attempts have been made, and considerable success is claimed for the most recent of them. The problem consists essentially of finding the field acting over a given element of volume, finding the polarisability of the matter in that element, multiplying them together, and then integrating the resulting vectors throughout space. None of these tasks is easy. The primary dipole is commonly regarded either as a partial ion-pair (which we have already seen is inadequate for another purpose, p. 52), or as a mathematical dipole placed somewhere along the valency, but it is improbable that either approximation holds well at close quarters, *i.e.*, within 1 or 2 A. The field acting at a point in the molecule will not be that of the primary dipole alone, but of it and all the moments which it has induced elsewhere in the molecule. Finally, the field induced by the primary dipole may react on the bond in which this occurs, which is always polarisable in some degree, and so gives in effect a modified primary dipole. The mean polarisability of bonded atoms in weak uniform fields is known; but the fields near polar bonds are not weak, and moreover, because they are not uniform it is really necessary to know the variation of the polarisability over the domain of the atom. The primary dipole has usually been treated as a mathematical one in order to be able to use the simpler field expression, and some reasonably plausible rule for placing it along the valency has been adopted. The field at a point was at first taken as that due to the primary dipole in a vacuum; later, some allowance was made for the effect of the intervening medium by dividing the field, in a vacuum, by the dielectric constant,[72] *i.e.*, assuming that the primary dipole and the point under consideration are embedded in a mass of uniform material. The effect of the field on the polarisable substance is then treated in one of several ways. The atom may be regarded as a polarisable point located at the nucleus, in which case the external field at its centre is multiplied by the atomic polarisability; or it may be assumed that, since the polarisation is mainly due to displacement of the outer electrons, the polarisable material is located at points in the valencies, and the field at these points along the valencies, determined by some plausible rule, is then multiplied by polarisabilities calculated for the bonds.[73] Recently a more elaborate treatment has been devised; it is designed to allow

[72] L. G. Groves and S. Sugden, *J.*, 1937, 1992.

[73] See *inter alia* papers by (*a*) (Mrs.) C. G. LeFèvre and R. J. W. LeFèvre, *J.*, 1936, 1130; G. C. Hampson and A. Weissberger, *J.*, 1936, 393; C. P. Smyth and G. L. Lewis, *J. Amer. Chem. Soc.*, 1940, 62, 721.

for the variation of the external field over the domain of the atom which is being polarised.[72] The projection of the supposedly spherical atom is divided into squares, the field in each of which is computed, and then the moment induced in an anchor ring generated by rotation of the circular projection about the axis of the primary dipole is derived ; finally, it is assumed that the ratio of the moment induced in the spherical atom to that induced in the anchor ring is the same as that of the volumes. Granting this assumption, made in order to convert a triple integral into a double one which can be evaluated graphically, it follows that the angle between the induced and inducing dipoles is the same in the anchor ring and the atom.

It is clear that no method has so far provided an exact treatment, and indeed there is little hope that this could be done with the present data and without more developed computing techniques than can commonly be employed. It is therefore important to assess the value of these comparatively easily applied methods. When the material in which the dipole is being induced is 5—6 A. away from the primary dipole, as at the other end of a benzene ring, they all give much the same result, so all of them can be trusted; but when the separation is only 1—2 A. they all give different results, and may therefore all be untrustworthy. An alternative statement is that if the induced moment is only one-tenth of the primary moment it can be accurately calculated, but if its ratio is 0·5 to 1·0 then probably it cannot be. The choice between the methods must be largely empirical, i.e., it must be decided by the internal and external consistency of the results; but it is not easy to apply tests. It is encouraging that the anchor ring method of Groves and Sugden gives tetrahedral values for the valency angles in methylene dichloride and chloroform,[74] in agreement with electron-diffraction results, when applied to the data for methyl chloride and these two compounds, although the other methods do not : but it leads [72] to a value for the C=O bond moment of 2·28 which is less than that of the C–O bond, 2·30, contrary to all expectation.

The phenomenon of dipole absorption by liquids occurs in the frequency range of the applied field between the limits where a polar molecule can still orient freely and follow the changing phase of the field perfectly, and where the friction between it and the surrounding molecules is so great that it has completely stopped orienting. Such absorption means that electromagnetic wave energy is being degraded to heat. It can give information about the size of the dipolar molecule, the viscosity of the liquid, and the magnitude of the

[74] L. G. Groves, J., 1938, 1197.

orienting dipole.[75, 76, 77]   An interesting example of its first applic-
ation comes from studies on some hydroxylic compounds, in which
it is found that absorption takes place at frequencies so high that
the molecule as a whole cannot rotate and therefore that it arises
from the rotation of the hydroxyl group independently of the main
bulk of the molecule.   The information about the effective micro-
scopic viscosity (which may differ from the bulk viscosity) shows that
it is relatively high for hydroxylic compounds, as is to be anticipated
from the known tendency of such compounds to associate through
hydrogen-bond formation.[75, 76]   It has occasionally proved useful as
an alternative method of measuring the moment; as, e.g., in the case
of certain proteins, for which results in good agreement with those
calculated from the dielectric increment were obtained.[77]   Although
both methods incorporate the same empirical relation, they are still
sufficiently different for this agreement to be impressive.   The very
large values obtained, of several hundred Debye units, are striking,
but they do not necessarily give much information about the struc-
ture of the protein molecule, because it is not known over what
portion of the molecule a single-electron transference may be made
to give the betaine structure responsible for the large moment, or
indeed if only one electron is transferred.

If the molecule were linear, and one electron were transferred from
end to end, a moment of 500 D., such as is found (the range is 300—
1200 D.), would correspond to a length of about 100 A., i.e., about
100 bond lengths projected on the axis of a zigzag chain.   Contri-
butions from side groups being neglected, the molecular weight of
such a molecule would be 1400—2000, which is only 2—3% of the
actual value.   This simple model of the dipolar molecule is therefore
incorrect.   If the molecule were a square sheet, with every group
bonded to four others, the molecule weight would indicate a side of
ca. 70 A.; if the pattern were a more open one, based on hexagonal
rings, the side would be about 100 A.   A single-electron transference
along a side or diagonal would then give a moment of the observed
order of magnitude.   If the molecule formed a hollow cube, the cube

[75] See ref. 48 (a), 48 (c), and 61 (a—l).

[76] (a) P. Debye, Chem. Reviews, 1936, 19, 171; (b) E. Fischer, Physikal.
Z., 1939, 40, 645; (c) E. Fischer and G. Klages, ibid., p. 721; (d) A. Budó,
ibid., p. 603; (e) K. Schmall, Ann. Physik, 1939, 35, 671; (f) H. Fricke and
L. E. Jacobson, J. Physical Chem., 1939, 43, 788; (g) E. Fischer and F. C.
Frank, Physikal. Z., 1939, 40, 345; (h) H. Müller, Ergebn. exakt. Naturw.,
1938, 17, 164; (i) P. Girard and P. Abadie, Physikal. Z., 1938, 39, 691;
(j) E. Plötze, Ann. Physik, 1938, 33, 226; (k) E. Keutner and G. M. Pota-
penko, Physikal. Z., 1937, 38, 635; (l) J. Malsch, ibid., 1936, 37, 849; (m)
G. Martin, ibid., p. 665.

[77] (a) J. L. Oncley, J. Amer. Chem. Soc., 1938, 60, 1115; (b) J. D. Ferry and
J. L. Oncley, ibid., p. 1123.

side would be about 30 A. or 42 A. for closed or open structures respectively. One-electron transference along a side, a face diagonal, or even cube diagonal, giving moments of 150—350 D., would suffice to explain the smaller moments observed, but not the medium or large ones. The results for circular or spherical models would be of similar orders of magnitude. If, therefore, the moments have real significance they show that there is not an electron transference along the whole length of a linear molecule, nor only a single-electron transference in a cubic model : but they do not by themselves allow of any choice between the other possibilities.

Dipole orientation can occur in solids, both crystalline and non-crystalline, but does not necessarily lead to dipole absorption. The polar molecules in certain solids, such as some forms of hydrogen bromide and hydrogen sulphide, have surprising freedom to orient in an external field, for dielectric constants as high as 20 or 40 are observed. This phenomenon is obviously of great value in studying the physics of crystals. Although there is a fair degree of correlation with the thermodynamic properties, and with molecular parameters, there is as yet no satisfactory quantitative theory of the effect.[78-81] Orientation in non-crystalline solids such as organic glasses or waxes can give rise to absorption. The phenomenon is of great practical importance, as one cause of dielectric losses in insulators at radio frequencies.[82, 83, 84] A quantitative theory of it, too, is as yet lacking.

(iii) *Atom Polarisation, the Orientation Polarisation of Flexible Molecules, and Molecular Vibrations.*

If a molecule is placed in a uniform electric field it becomes " polarised "; *i.e.*, relative to its former state it develops an electric moment which reduces its potential energy in the field.

The polarisation is commonly considered to arise by three independent processes, known as *electron*, *atom*, and *orientation* polarisation. The first occurs because the electrons are pulled one way and nuclei another, so the original distribution of electrons round nuclei is elastically distorted. The second occurs if the molecule contains

[78] See (a) C. P. Smyth, *Chem. Reviews*, 1936, **19**, 329; (b) A. Eucken, *Z. Elektrochem.*, 1939, **45**, 126.

[79] (a) W. O. Baker and C. P. Smyth, *J. Amer. Chem. Soc.*, 1939, **61**, 1695; (b) *idem, ibid.*, p. 2063; (c) *idem, J. Chem. Physics*, 1939, **7**, 574; (d) *idem, J. Amer. Chem. Soc.*, 1939, **61**, 2798.

[80] (a) A. H. White and W. S. Bishop, *ibid.*, 1940, **62**, 8; (b) A. H. White, B. S. Biggs, and S. O. Morgan, *ibid.*, p. 16.

[81] A. Müller, *Proc. Roy. Soc.*, 1937, *A*, **158**, 403; 1938, *A*, **166**, 316.

[82] E. B. Moullin, *J. Inst. Elect. Eng.*, 1940, **86**, 113.

[83] D. R. Pelmore and E. L. Simons, *Proc. Roy. Soc.*, 1940, *A*, **175**, 253, 468.

[84] F. C. Frank and W. Jackson, *Trans. Faraday Soc.*, 1940, **36**, 440.

dipolar bonds; for then the atoms bearing an effective negative charge will be pulled in the opposite way from those bearing an effective positive charge. Hence, a dipolar bond may change its length, or the angle between two such bonds may be changed. Both of these processes are functions of the field strength and of elastic constants of the molecule alone.

The third type of polarisation occurs if the molecule as a whole has a permanent electric dipole moment, which is there even when there is no external electric field. It occurs by the twisting of the polar molecule in the field under the action of a couple. If all the molecules were to twist freely, the smallest external field would suffice to align them all and bring about a high degree of order. Thermal collisions tend to preserve disorder, however, and hence it is said that thermal effects oppose the field. From these considerations it may readily be seen that, whereas electron and atom polarisabilities depend only upon the nature of the molecule, orientation polarisability should decrease as the temperature rises. Furthermore, owing to the very different damping influences which would affect electrons, atoms, and molecules if an alternating field were applied, it would not be expected that the three kinds of polarisation should all contribute at all frequencies. Orientation should cease in the ultra-short radio-wave region in liquids or in the far infra-red in gases, atom polarisation should cease before the visible frequencies are reached, but electron polarisation could go on until the hard X-ray frequencies are reached.

The expected dependence of polarisation * upon temperature and upon frequency of the applied field is realised; for if the polarisation of a molecule is not different at infra-red and at medium radio frequencies, then neither is it dependent upon temperature, and conversely; and, furthermore, while the polarisations of dihomoatomic molecules such as those of hydrogen, nitrogen, and oxygen are not appreciably different at the visible and the infra-red frequencies, those of polar molecules such as hydrogen chloride, or of non-polar molecules with opposed polar bonds (e.g., carbon dioxide) are different. The foregoing picture of polarisation as occurring by three independent processes thus appears adequate and acceptable.[(ii) 48, 54]

When the polarisation of a compound such as ethylene dichloride is considered, fresh problems seem to arise. If the molecule were fixed in the trans-position, by dipole–dipole or by "exchange" forces, it would be non-polar, and would undergo only electron and atom polarisation, as does trans-dichloroethylene; but if the two

* The words "polarisability" and "polarisation" are commonly used interchangeably.

halves could rotate freely relative to each other, then there would be molecules with every conceivable configuration, and therefore with dipole moments varying continuously from zero to a maximum value μ_{max}. It can easily be shown that if all configurations are equally probable, the mean polarisation $4\pi N\bar{\mu}^2/9kT$, corresponds to a mean moment $\bar{\mu}$ of $(1/\sqrt{2})\mu_{max}$. If rotation were not perfectly free, but if fixation in the *trans*-position were nevertheless incomplete, $\bar{\mu}$ would have a value intermediate between 0 and $(1/\sqrt{2})\mu_{max}$. Moreover, since the configurations of higher potential energy are also those of higher moment, as the relative importance of these would increase with rising temperature, so too would the moment. The theoretical work which has been done on this problem falls into several periods.

At first, the aim was to derive an expression, by classical methods, for the mean moment or polarisation as a function of temperature if it were assumed that the main forces between the rotating groups are between the dipoles therein.[1] Later work consisted in elaborating the classical treatment to take into account the momentum coordinates which showed that if there is a change in the moments of inertia with configuration some configurations will be more favoured than others. Crudely speaking, it is found that the spinning ethylene dichloride molecule, to take a concrete example, tends to spin as nearly as possible about the line joining its main masses, the chlorine atoms, and to reduce its moment of inertia about this axis; so the *trans*-configuration is favoured. The factor representing this effect, by which the exponential term representing that of potential energy is multiplied, is called the statistical weight factor. Quantum mechanics was also applied to the problem, and besides providing an equivalent weight-factor representing the variation in the density of quantum states with configuration, it showed that at low temperatures the effect of zero-point energy is important. In all these later treatments the potential function taken had to be one with simple mathematical properties, rather than one derived from a physical model of the molecule. It was hoped that the application of these theoretical results to experimental data would make possible the calculation of parameters expressing the intramolecular forces between the rotating groups. It was realised that these are probably not dipole–dipole forces alone, and that it is most desirable to investigate them experimentally.[2, 3, 4]

[1] See refs. (ii) 48 (d, e); and article by K. L. Wolf and O. Fuchs in Freudenberg's " Stereochemie," Vienna, 1932, p. 774.

[2] J. E. Lennard-Jones and H. H. M. Pike, *Trans. Faraday Soc.*, 1934, 30, 830.

[3] W. Altar, *J. Chem. Physics*, 1935, 3, 460.

[4] J. Y. Beach and D. P. Stevenson, *ibid.*, 1938, 6, 635.

In this concentration upon one part of the problem, the nature of the polarisation process as a whole in flexible molecules was over-looked. There seems to have been no clear realisation that atom polarisation and the orientation polarisation of molecules bent by thermal collision are one and the same thing. On a crude dynamic view it appeared indeed that they are distinct, for it would seem that, if the period of bending were large compared with the time of relaxation of the molecule, there should be both orientation and atom polarisation; whereas if it were small there should still be atom polarisation (in addition to electron polarisation).[5] The absurdity of this view became obvious, however, on considering what the polarisation of a freely rotating molecule would be; for, since it is greater the smaller the force constant resisting distortion, in such a molecule it should obviously be infinite, which it certainly is not.

The expression for atom polarisation can be derived in classical mechanics, which is adequate for the purpose,[(ii)][54] by finding the average displacement $\bar{x}$ caused by a field F, and multiplying this by $4\pi N e_i / 9F$, where e_i is the effective charge moved.

Thus

$$P_A = \frac{4\pi N e_i}{9F} \cdot \frac{\int_{-\infty}^{+\infty} x e^{-V(x)/kT + e_i x F/kT} dx}{\int_{-\infty}^{+\infty} e^{-V(x)/kT + e_i x F/kT} dx} \quad . \quad . \quad . \quad (1)$$

where $V(x)$ is the potential energy for a displacement x.

The expression for the orientation polarisation of a molecule such as ethylene dichloride is obtained by substituting a mean value of μ^2 in the relation between P_0 and μ. The latter is obtained by one averaging process expressed thus :—

$$P_0 = \frac{4\pi N}{3F} \cdot \frac{\int \mu e^{\mu F \cos\theta/FT} \cos\theta \sin\theta . d\theta . d\phi}{\int e^{\mu F \cos\theta/kT} \sin\theta . d\theta . d\phi} \approx \frac{4\pi N \mu^2}{9kT} \quad . \quad (2)$$

where θ is the inclination of the instantaneous moment of the molecule to the axis of the applied field F, and ϕ is the remaining angular co-ordinate for the three-dimensional problem.[48] Another averaging process gives

$$\bar{\mu}^2 = \frac{\mu^2_{max}}{4} \cdot \frac{\int \psi^2 e^{-V(\psi)/kT} d\psi}{\int e^{-V(\psi)/kT} d\psi} \quad . \quad . \quad . \quad (3)$$

where ψ is the angular displacement from the *trans*-configuration, and $V(\psi)$ expresses the potential energy in terms of it.

⁵ (a) A. E. Finn, G. C. Hampson, and L. E. Sutton, *J.*, 1938, 1254; (b) D. Ll. Hammick, G. C. Hampson, and G. I. Jenkins, *ibid.*, p. 1263; (c) I. E. Coop and L. E. Sutton, *ibid.*, p. 1269.

Now the general expression for the complete, mean polarisation of a flexible molecule is : [6]

$$P = \frac{4\pi N}{3F} \cdot \frac{\int \mu(\psi) e^{-V(\psi)/kT + \mu(\psi)F\cos\theta/kT} \cos\theta \cdot d\psi \cdot \sin\theta \cdot d\theta \cdot d\phi}{\int e^{-V(\psi)/kT + \mu(\psi)F\cos\theta/kT} d\psi \cdot \sin\theta \cdot d\theta \cdot d\phi} \quad . \quad (4)$$

where $\mu(\psi)$ expresses μ as a function of ψ.

This includes the effect of internal potential energy, field, permanent moment [now defined as the constant term in $\mu(\psi)$] and temperature. It therefore gives the whole of the polarisation except the electron polarisation, which would require further internal co-ordinates and potential functions and has been omitted for simplicity. It can immediately be seen that (4) is the general form of (1), and also that it is composed of the two stages represented by (2) and (3). Consequently the polarisations visualised from the two different dynamical pictures are statistically indistinguishable. In the special case when $\mu = \mu_1\psi$ and $V(\psi) = V_0\psi_1^2/2$, $P = 4\pi N\mu_1^2/9V_0$. For oscillations of small amplitude, when both of these conditions are usually satisfied, the polarisation is independent of temperature, but if μ depends less simply upon ψ, or if there is any anharmonicity, the polarisation is temperature-sensitive. This clarification of the principles is a necessary preliminary to the consideration of detailed results, which may now be undertaken.

It has long been realised that undetermined atom polarisation may give rise to appreciable, and even serious error in the determination of electric dipole moments by the common method of taking the orientation polarisation as the difference of the total polarisations at radio and visible frequencies. Extrapolation of the latter, *i.e.*, the molecular refractivity, to infinite wave-length from observations in the visible range obviously cannot remove the error, because these data are unaffected by absorptions in the infra-red region, where atom polarisation is first manifested. Unless, therefore, the polarisation can be studied over a range of temperature, or the refractivity can be followed through the infra-red, as has been possible so far only for relatively few of the many substances investigated (p. 53), atom polarisation must be either ignored or assessed empirically. From studies of the polarisations of compounds with known P_A and P_E, various authors concluded that P_A is about 5—15% of P_E.[(ii) 67, 68] Hence, it came about that atom polarisation was frequently regarded as a nuisance, but hardly ever as a major phenomenon. It is now known, however, that this is not true, for such polarisation can be large and of possible importance as a means of determining certain molecular parameters. It can be large, not only in molecules of the

[6] N. R. Davidson and L. E. Sutton, *J.*, 1939, 347.

ethylene dichloride type, in which small moments are held opposed by relatively weak forces, but also in those wherein strongly dipolar bonds or groups are held opposed to one another by ordinary valency forces.

From the early days of dipole measurements it was known that some molecules which ought not to be polar appeared in fact to be so; *i.e.*, they showed differences between their radio- and visible-frequency polarisations which, since they were 20—40% of P_E, appeared not to be atom polarisation. Examples of this are poly-nitrobenzenes, *p*-benzoquinone, metallic acetylacetonates, and other co-ordination compounds. The measurements had been made in solution, and it was therefore suspected that the anomalies might be due to a solvent effect. Two possible ways in which this could come about were suggested.[7, 8] In 1938,[5(c)] however, it was shown that these anomalous polarisations were just as great in the vapour phase, and furthermore, that they were independent of temperature. It was therefore concluded that they must after all be atom polarisations.*

This conclusion was further supported by a quantitative examination of the data. Molecules which contained the same polar groups, able to oscillate in the same way, should have equal atom polarisations. The anomalous polarisations for cyanogen, *trans*-dicyano-ethylene (fumaronitrile), and *p*-dicyanobenzene are in fact 8·3, 9·8, and 11·9 c.c., respectively;[5(c), 9, 10] and those for several symmetrical *p*-benzoquinones, tetramethyl*cyclo*butanedione, and carbon sub-oxide are all 8—10 c.c. Next, when the appropriate relation between P_T—P_E, μ (the vibrating moment), and V_0 (the force constant of bending) was used to calculate any one of these quantities from experimental values of the other two, a value in agreement with an experimental value of it, or of reasonable magnitude, was obtained in almost all instances. Finally, by using the force constant derived on the assumption that the polarisation in *p*-benzoquinone arises from vibration of the C=O bonds perpendicular to the plane of the double bond, and taking the appropriate reduced mass, a period of $3·0 \times 10^{-13}$ sec. was calculated for this mode of vibration. The experimental value is $2·8 \times 10^{-13}$ sec.[5(c)]

The general conclusions are that, since the mechanism of atom or

[7] (a) H. O. Jenkins, *J.*, 1936, 862; (b) S. H. Bauer, *J. Chem. Physics*, 1936, **4**, 458.

[8] F. C. Frank and L. E. Sutton, *Trans. Faraday Soc.*, 1937, **33**, 1307.

[9] H. E. Watson and R. L. Ramaswamy, *Proc. Roy. Soc.*, 1936, *A*, **156**, 144.

[10] See forthcoming paper by G. I. M. Bloom and L. E. Sutton.

* At that time the unreality of the distinction between this and the polarisation of molecules bent by thermal impact was not realised; so the relative merits of the two theories were gravely debated.

vibration polarisation is unrelated to that of electron polarisation, no simple numerical relation can be expected. Although the empirical rule that P_A is 5—15% of P_E holds reasonably well for compounds containing polar bonds with less than 2·5 D., it fails if the bond moments are greater. In general, too, it is not an additive function of atoms, although rough additivity may be observed in a series of related compounds such as the di-, tri-, and tetra-acetylacetonates of certain metals. Compounds with essentially the same oscillating systems have the same vibration polarisation. From observed vibration polarisations it is frequently possible to calculate the force constant of vibration, and by combining this with an observed frequency of vibration it may be possible to elucidate the mode of vibration. To allow for P_A in a determination of dipole moment, the best procedure is to calculate it roughly by using the relation $P_A = 4\pi N\mu_1^2/9V_0$ (μ_1 = vibrating moment, V_0 = force constant) for each one-dimensional oscillation in the molecule; but if the component moments are less than 2·5 D., the 5% rule can be applied with sufficient accuracy.

If the term atom polarisation is to be retained it is best applied to the temperature-invariant polarisation arising from vibrations of small amplitude, as has been done in the foregoing section. The term " vibration polarisation " may then be used in a more general sense to include both this and the temperature-variant polarisation arising from oscillations of large amplitude. Some of the problems connected with the analysis of experimental data in order to derive a potential function for these oscillations have already been indicated. When the important mode of vibration is a partial rotation about a single bond the potential function is likely to be complicated. The ideal procedure would be to derive it directly from the data and then to analyse it into its constituent terms, such as dipole–dipole interaction, dispersion forces, and exchange forces. This has been done only in so far as that if the observed moment is $(1/\sqrt{2})\mu_{max}$ and is temperature-invariant, the function is presumed to be one with values always much less than kT. In general, it is impracticable : so usually, a function is assumed, possibly as a result of considering the probable interatomic forces; it is then tested, and if it does not fit it may be adjusted until an improvement is effected.[2, 3, 4, 10] Such a trial-and-error method could give a unique solution (cf. the procedure of direct comparison for analysing electron-diffraction photographs) if enough curves were tried, and if the vibrations were sufficiently large for the whole of the curve to be explored. The available temperature range is, however, usually so small that only a part can be followed, and therefore there is little point in trying many curves. This limitation has been realised with increasing

clearness by workers in the subject, but it may be further emphasised. The figure shows typical potential curves which have been tested [4, 10] against the data for ethylene dichloride—so far the most carefully investigated substance of this type. The clear area represents the region within which $kT > V(\psi)$. Although the importance of the molecules with the larger values of ψ is relatively greater, because they make larger contributions to the polarisation, the exponential falling off in the number of molecules in these configurations is decisive, and consequently little is known about the shape of the
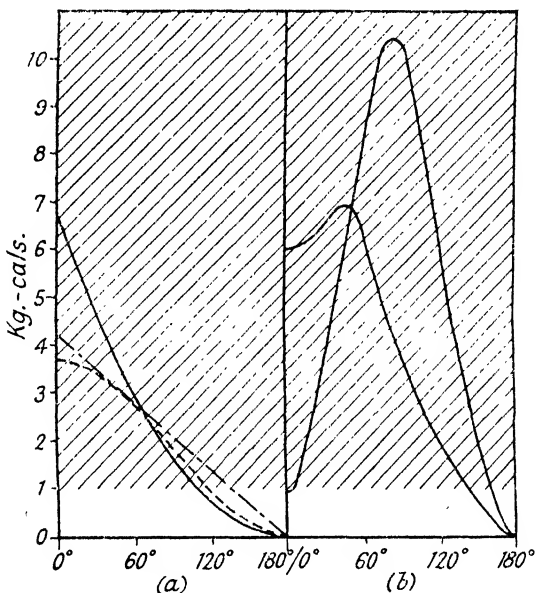
curve above the fringe of the shaded " veil of ignorance ". Nevertheless, in spite of this limitation, which applies also to electron-diffraction studies, useful conclusions have been reached from determinations of the lower portions of the curves. The combined results of the two experimental methods show that the repulsions between the groups in the ethylene dihalides are not predominantly due to C–Hal dipole–dipole forces but to exchange forces between the several possible pairs of atoms, commonly called " steric " forces. They are greater in ethylene chlorobromide than in ethylene chloride, and still greater in ethylene dibromide,[4, 10, 11] which is the order of increase of halogen diameter but not of C–Hal moment.

Vibration polarisation thus far seems a satisfactory explanation

[11] (a) J. Y. Beach and K. J. Palmer, *J. Chem. Physics*, 1938, **6**, 639; (b) J. Y. Beach and A. Turkevich, *J. Amer. Chem. Soc.*, 1939, **61**, 303.

of the facts.   The Raman spectra have, however, been interpreted to mean that there is an equilibrium between molecules of these substances fixed in *cis*- and *trans*-configurations.[12]   Because this hypothesis seemed inherently less probable, the polarisation data have not hitherto been used to test it, but an interesting result is found when this is done.

It is clear [13] that if V_π is the difference of energy between the *trans*- and the *cis*-form, and s is the ratio of the weight factors, then $N_{trans}/N_{cis} = se^{V_\pi/RT}$ whence $\log_e N_t/N_c - \log_e s = V_\pi/RT$, so if $\log_{10} N_t/N_c$ is plotted against $1/T$ a straight line should be obtained. This can be done because N_t/N_c can be calculated from $P_{obs.}$ if assumptions be made about the magnitude of the rotating moment; and it results in surprisingly good straight lines, both for solution and for vapour data, which intersect the ordinate axis to give values for s favouring the *trans*-form, as is expected.[10]   Hence it appears that existing polarisation data support this hypothesis; but it can be shown that they are really somewhat ambiguous.   On the *trans* oscillation theory the equivalent plot would be of $\log_{10}(1-\rho)/(1+\rho)$ * against V_π/RT, and the form of this curve can be calculated for possible potential functions.   It is found that, although the cosine, linear, or parabolic functions do not give rectilinear curves, the curvature over ranges which correspond to the V_π' calculated and the ΔT employed is usually small, and might be barely detectable.[10] It is therefore clear that, until polarisation measurements over a wider range of temperature are available, no choice between the theories can be made.   Electron-diffraction studies are similarly indecisive, because the proportion of the *cis*-isomer would be small.

A parallel suggestion, also based on Raman spectra studies, has been made that acetylene tetrachloride consists of a *cis*-form and two others formed by relative rotation of the groups through 120° either way, and that the difference of potential energy is 1·1 kg.-cals.[13]   This can be definitely rejected, for the molecule would then be much more polar than in fact it is; and this conclusion is supported by electron-diffraction results.[14]   The latter, also, are in disagreement with the further suggestion that *cyclo*hexane is flat.[15] Polarisation measurements have not so far given any information about the forces between the non-bonded hydrogen atoms in ethane-like molecules.

[12] A. Langseth, H. J. Bernstein, and B. Bak, *J. Chem. Physics*, 1940, **8**, 415.
[13] A. Langseth and H. J. Bernstein, *ibid.*, p. 410.
[14] V. Schomaker and D. P. Stevenson, *ibid.*, p. 637.
[15] A. Langseth and B. Bak, *ibid.*, p. 403.

* ρ (see 4) is an average value of cos ϕ, where ϕ is the angle between the moments of the two halves of the molecule projected on to a plane perpendicular to the axis of rotation.

Other points of interest in relation to interatomic forces and molecular structure which have recently emerged are the following. If the radius about which bound chlorine atoms rotate is sufficiently large, as in oo'-dichlorodiphenyl, it appears that London dispersion forces of attraction may cause the *cis*-position to be favoured so far as steric forces allow.[16]

Measurements on benzil have been interpreted to mean that the molecule has the two benzoyl groups fixed skew at approximately 90°; because the moment is equal to that for free rotation, *viz.*, $(1/\sqrt{2})\mu_{max}$, and is temperature-invariant, yet in the analogous stilbene dichlorides and hydrobenzoins rotation is far from being free as is shown by the difference between the mean moments for the racemic mixture of enantiomorphic forms and for the *meso*-form.[17]

The electric moment of hydrogen peroxide in dioxan solution agrees with the skew right-angled configuration predicted for it from the interaction between the electron clouds round the oxygen atoms,[(i) 4] but it is not by itself decisive. An X-ray examination of the liquid structure is, however, more definitely favourable.[18] Both the electron-diffraction and the electric-moment evidence relating to the freedom of rotation about the S–S bond in hydrogen disulphide, dimethyl disulphide,[19, 20] and sulphur monochloride [20, 21] are inconclusive. The moment of hydrazine agrees with that predicted for a fixed skew configuration,[(i) 4] as do those of some alkyl and aryl derivatives.[22] The infra-red absorption of hydrazine [23] also leads to the conclusion that it has the configuration required by Penney and Sutherland's theory.[(i) 4]

Inhibition or reduction of rotation about a single bond, owing to resonance with a double-bonded structure, apparently occurs in certain esters, but not in all, as is shown by the magnitude and the temperature characteristics of the polarisation.[24, 25] The facts that the diacetyl potential function is a parabolic one with the large potential barrier (V_π) of *ca.* 23 kg.-cals., indicate that there is similar stiffening in this molecule.[10] Electron-diffraction evidence shows

[16] G. C. Hampson and A. Weissberger, *J. Amer. Chem. Soc.*, 1936, **58**, 2111.

[17] C. C. Caldwell and R. J. W. Le Fèvre, *J.*, 1939, 1614.

[18] J. T. Randall, *Proc. Roy. Soc.*, 1937, *A*, **159**, 83.

[19] D. P. Stevenson and J. Y. Beach, *J. Amer. Chem. Soc.*, 1938, **60**, 2872.

[20] C. P. Smyth, G. L. Lewis, A. J. Grossmann, and F. B. Jennings, III, *ibid.*, 1940, **62**, 1219.

[21] K. J. Palmer, *ibid.*, 1938, **60**, 2360.

[22] H. Ulich, H. Peisker, and L. F. Audrieth, *Ber.*, 1935, **68**, *B*, 1677.

[23] N. F. Fresenius and J. Karweil, *Z. physikal. Chem.*, 1939, *B*, **44**, 1.

[24] R. J. B. Marsden and L. E. Sutton, *J.*, 1936, 1383.

[25] S. Mizushima and M. Kubo, *Bull. Chem. Soc. Japan*, 1938, **13**, 174.

the fixation even more definitely, both in this compound and in glyoxal.[26]   It is not possible to show its existence in $\alpha\gamma$-butadiene.[27]

The mutual repulsion of rotating groups falls rapidly if the separation is increased above one bond length; although certain complications arise from doing this in practice, since it necessitates either introducing further axes of rotation or placing a benzene ring between the groups.   The rate of fall depends partly upon the polarity of the groups; and, as might be expected, it is less if they are highly polar (*e.g.*, $CH_2 \cdot CN$) than if they are but weakly so (*e.g.*, CH_2Br, OCH_3, NH_2).[28, 29, 30]

It is premature to say that the experimental data have been completely interpreted; they frequently are too meagre as yet to give very definite answers to all the questions which it is hoped they may settle.   The full nature of the forces between rotating groups, and the way in which they are affected by the medium when a solvent is present, have yet to be fully elucidated.

(iv) *The Application of Electric Dipole Moment Measurements and of the Diffraction of Electrons by Vapours to the Study of Molecular Structure.*

The potentialities of the foregoing experimental methods have frequently been explained in review articles,[31, 32] and to some extent they have been taken for granted in the previous section, but for convenience they may be summarised afresh.

The information forthcoming from an electron-diffraction study is comprised in the perfect radial distribution curve.   It is a list of all the possible interatomic distances in which each item is tagged according to the scattering powers of the two atoms to which it refers.   Since the scattering factors are known, it is frequently possible, in simple molecules, to discover to what pair of atoms each distance refers, and thus to elucidate the complete spatial distribution of the nuclei.   In favourable cases it is therefore possible to give very exact and complete answers to questions of stereochemistry involving interatomic distances though not of order in space, for enantiomorphs obviously give the same diffraction pattern.   For large molecules the method usually is not so useful, for it gives so

[26] J. E. Lu Valle and V. Schomaker, *J. Amer. Chem. Soc.*, 1939, **61**, 3520.

[27] V. Schomaker and L. Pauling, *ibid.*, p. 1769.

[28] Ref. (ii) 48 (*e*), p. 402; also (ii) 48 (*f*), Chap. V.

[29] J. A. A. Ketelaar and K. J. Palmer, *J. Amer. Chem. Soc.*, 1937, **59**, 2470.

[30] P. Trunel, *Ann. Chim.*, 1939, **12**, 93.

[31] See refs. (Section i) 1, 2, 3, 6, 7, 9, 14, 35; 4, 5, 48.

[32] (*a*) C. P. Smyth, *J. Org. Chem.*, 1936, **1**, 17; (*b*) *idem*, *Pubns. Amer. Assoc. Adv. Sci.*, No. 7, " Recent Advances in Surface Chemistry and Chemical Physics," 1939, **98**.

many data that they cannot be disentangled. When the molecule is highly symmetrical this difficulty may, however, be overcome.

It is also possible, as a general rule, to discover whether two atoms are bonded covalently or not : if they are 3 A. or more apart they are not bonded effectively.[33] The usefulness of this criterion is greatly augmented by the empirical rule that the covalent radius of an atom is constant to a first approximation. Exceptions to this rule have been interpreted to mean that the bond is not what it was thought to be, *i.e.*, that it is not of the supposed order (single, double, or triple), or that the orbitals used in it are not those used in the majority of the covalent bonds which the two atoms in question usually form, *e.g.*, that it may be ionic, or that, let us say, *d* orbitals may be used in addition to *s* and *p* orbitals. Electron-diffraction studies have therefore been very extensively and intensively employed to investigate bond character and so to detect the phenomenon of wave-mechanical " resonance " in molecules.

The electric dipole moment measures the asymmetry of distribution of the negative charge relative to the positive in a molecule. It is a vector quantity, and for many purposes may be considered as the vector sum of moments characterising the individual bonds. They are not particularly characteristic, for they can often react on each other very markedly by induction : [35] nevertheless, it is possible to visualise and in some degree to calculate the primary, undisturbed moment of a bond. The vector character of the total moment obviously makes it a function of the molecular symmetry. Stereochemical problems can therefore be elucidated even in quite large molecules, provided that the problem in question is related in a simple way to the symmetry of the molecule; examples of this will occur later.

Since the moment of a polar molecule, group, or bond is a measure of the electrical asymmetry therein, it has often been used to study problems related to the distribution of valency electrons. Attempts have been made to correlate the moments of bonds with the differences between electronegativity co-ordinates characteristic of the atoms : [36] they have met with considerable qualitative success, but it is not yet possible to predict the moment of a bond with nearly as much accuracy as its length. The magnitude of the

[33] See ref. (i) 35 (p. 154).

[34] N. V. Sidgwick, *Chem. Reviews*, 1936, **19**, 183.

[35] L. E. Sutton and L. O. Brockway, *J. Amer. Chem. Soc.*, 1935, **57**, 473.

[36] (a) J. G. Malone, *J. Chem. Physics*, 1933, **1**. 197; (b) M. G. Malone and A. L. Ferguson, *ibid.*, 1934, **2**, 99; (c) C. P. Smyth, *J. Physical Chem.*, 1937, **41**, 209; (d) *idem*, *J. Amer. Chem. Soc.*, 1938, **60**, 183; (e) F. T. Wall, *ibid.*, 1939, **61**, 1051; 1940, **62**, 800; (f) H. C. Brown, *ibid.*, 1939, **61**, 1483; (g) K. L. Wolf and H. Harms, *Z. physikal. Chem.*, 1939, *B*, **44**, 359.

moment of a bond, group, or molecule may also be used to elucidate major problems concerning their structure, as in the cases of the *iso*cyanides [34] and the proteins (see p. 56).

By comparing the observed moment of a system with the value anticipated for it from the roughly known values of bond moments it is possible to detect abnormal electron distributions. The algebraic differences of moment between aliphatic and aromatic, ethylenic, or acetylenic compounds have been correlated with the electron displacements consequent upon wave-mechanical resonance.[37] The logical basis of the use of abnormalities of either bond-length or electric moment to establish the reality of this phenomenon is the same. If, in a large number of compounds abnormalities are found which are in the sense predicted from the resonance hypothesis then, although other effects may cause abnormalities which occasionally confuse or obscure the issue, we may reasonably conclude that the hypothesis is correct, and that it is an essential part of the truth though not necessarily the whole truth. Agreement in a few isolated cases means nothing, but agreement in a large number is significant : and agreement between independent experimental methods is still more significant.[i] [6] It is on such a statistical basis of substantial agreements that the experimental case for the existence of resonance rests. One further general remark about the characteristics of dipole moments and of bond lengths may be made. The moment of a bond is generally more sensitive to disturbances than is its length. The percentage change caused in the former by resonance (unless it introduces no fresh electronic asymmetry) is generally greater than in the latter, and the presence of nearby polar bonds also has much more effect. This means that such disturbances are easier to detect, but also easier to confuse : and so it lays further emphasis on the desirability of not relying on one method alone.

Stereochemistry.—There have been several interesting recent advances not yet reported upon.

It has been possible from electron-diffraction studies to assign spatial configurations to many simple organic and inorganic molecules of the type AB_2, AB_3, AB_4, AB_5, and AB_6.[38] These configuration are supported by the electric moments when both data are available. A recent example is that tellurium tetrachloride has been shown to have an apparent moment of 2·54 D. in benzene

[37] (a) Refs. (ii) 48 (*f*), 72; (b) L. E. Sutton, *Trans. Faraday Soc.*, 1934, **30**, 789; (c) L. E. Sutton and R. J. B. Marsden, *J.*, 1936, 599; (d) D. I. Coomber and J. R. Partington, *J.*, 1938, 1444; (e) H. L. Goebel and H. H. Wenzke, *J. Amer. Chem. Soc.*, 1937, **59**, 2301; (f) *idem, ibid.*, 1938, **60**, 697; (g) J. A. C. Hugill, I. E. Coop, and L. E. Sutton, *Trans. Faraday Soc.*, 1938, **34**, 1518.

[38] See N. V. Sidgwick and H. M. Powell, *Proc. Roy. Soc.*, 1940, *A*, **176**, 153.

solution,[39] which, since it is too large to be explained as atom polaris-
ation on probable values of μ, or V_0 (p. 62), is probably real and shows
that the molecule is unsymmetrical. The electron-diffraction
pattern indicates a distorted pyramidal structure, such as might
be derived from a trigonal-bipyramidal arrangement of five valencies
with one of them—probably equatorial—occupied by an unshared
pair of electrons.[40]

The configurations are in general agreement with quantum-
mechanical theories of directed valency,[41] but they may also be
successfully correlated on simple principles which are more readily
applied by the chemist.[38] These are (1) that a fully-shared valency
group has the most symmetrical of the possible arrangements;
(2) if the stereochemical arrangement corresponding to a fully-shared
valency group is known, the configuration of a molecule with a group
of the same size, but with some of the electrons unshared, can be
derived by supposing that each pair of unshared electrons fills the
place of a covalency. These rules are very satisfactory except for
compounds of the transitional elements, for which it is less easy to
define the term " valency group ".

Electron-diffraction work on compounds of the type SOX_2,
SO_2X_2,[21] POX_3,[42] and PSX_3,[43] where X is a halogen, indicate that the
valencies are not directed along the axes of a regular tetrahedron,
but that the XSX or XPX angles are less, while the OSO angle is
greater, than $109° 28'$. This change is the opposite of that to be
expected from steric repulsion forces, and therefore it is presumed
to mean that the bonds are not all single. This conclusion is
supported by the evidence of bond lengths and bond moments (p. 73).

It may be mentioned that in the silicon analogues of methylene
chloride and chloroform the Cl–Si–Cl angle was found to be $110° \pm$
$1°$[44] and therefore not to show the effects of repulsion between chlorine
atoms which are observed in the carbon compounds, where the angle
is $121° \pm 2°$.[35] This is to be expected, since the central atom is
larger and the Cl–Cl distance is consequently greater in the former
compounds.

One more of the classical stereochemical problems in organic
chemistry has finally been settled by dipole-moment measurements.
It has been shown that the labile and stable forms of several sub-

[39] C. P. Smyth, A. J. Grossmann, and S. R. Ginsburg, *J. Amer. Chem. Soc.*,
1940, **62**, 192.

[40] D. P. Stevenson and V. Schomaker, *ibid.*, p. 1267.

[41] (a) See ref. (i) 35, Chap. III; (b) G. E. Kimball, *J. Chem. Physics*, 1940,
8, 188.

[42] L. O. Brockway and J. Y. Beach, *J. Amer. Chem. Soc.*, 1938, **60**, 1836.

[43] J. Y. Beach and D. P. Stevenson, *J. Chem. Physics*, 1938, **6**, 75.

[44] L. O. Brockway and I. E. Coop, *Trans. Faraday Soc.*, 1938, **34**, 1429.

stituted phenyldiazocyanides are stereoisomers of each other and that the configurations allotted to them from their chemical properties are correct, the former being *cis* and the latter *trans*.[45] The experimental method employed was that of substituting a linear polar group in the para-position and determining the effect on the moment. It was fortunate that the *cis*-form of azobenzene had been discovered a short time previously,[46] since its moment was necessary for the proper interpretation of the other data. Its high polarity ($\mu = 3\cdot0$ D.) agrees with the X-ray evidence [47] that it is indeed the *cis*-compound.

The proof, from the polarisations of the vapours, that *p*-dinitrobenzene and beryllium acetylacetonate are non-polar [5(c)] shows that, as required by the wave-mechanical concept of resonance, the nitro-group has an axis of symmetry along the bond joining it to other groups, and that the acetylacetonate ring is planar and has an axis of symmetry passing through the metal atom and the middle carbon atom. The symmetry of the nitro-group is demonstrated further by dipole and electron-diffraction studies on tetranitromethane.[48]

It is to be expected that compounds of the type (I) will be flat if the valency angle of X is greater than 120°, and bent along the line X—X if it is less than 120°, and if X is CH_2, O, S, or Se [49] it is clear that a flat structure means a non-polar molecule, while a bent one will be polar if the Ph—X bonds are polar. Dipole evidence shows that except when X is O, the molecule is bent. The exception has been explained as a result of resonance. From this it might be expected that if X is >NMe, a similar result would be found.[50] The evidence is inconclusive, however, for there is a small moment of $0\cdot4$ D.[49] which may indicate that the ring system is bent, or that this is flat but that the nitrogen bonds are non-planar and there is *cis-trans*-isomerism, with the *cis*-form polar.

The development of methods whereby the valency angle of an atom or group X in the compound XPh_2 can be determined, and allowance made for certain interactions which cause error, has been reported upon previously.[4] One further possible cause of error, the
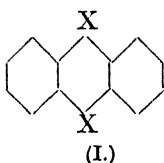
[45] R. J. W. Le Fèvre and H. Vine, *J.*, 1938, 431.

[46] G. S. Hartley, *J.*, 1938, 633; G. S. Hartley and R. J. W. Le Fèvre, *J.*, 1939, 531.

[47] J. M. Robertson, *J.*, 1939, 232.

[48] A. J. Stosick, *J. Amer. Chem. Soc.*, 1939, **61**, 1127.

[49] (Miss) I. G. M. Campbell, (Mrs.) C. G. Le Fèvre, R. J. W. Le Fèvre, and E. E. Turner, *J.*, 1938, 404; see also ref. (4) (p. 37).

[50] L. E. Sutton and G. C. Hampson, *Trans. Faraday Soc.*, 1935, **31**, 945.

effect of solvent, has now been eliminated by a series of polarisation measurements on the vapours of diphenyl ether and suitable derivatives, which give a value of $124° \pm 5°$.[51] This is a reasonable agreement with that of $128° \pm 4°$ from solution measurements [50] and also with one of $118° \pm 3°$ obtained from an electron-diffraction study of pp'-di-iododiphenyl ether.[52] The angle is therefore certainly near $120°$ in these ethers, and not $110°$ or less as in aliphatic ethers, or other oxygen compounds. This agrees with one of the deductions from the " resonance " hypothesis.[50] There is as yet little evidence to show whether or not another deduction—that the benzene rings may be coplanar—is correct, but some dipole evidence has been interpreted to mean that they are not, and that the plane of one is perpendicular to that of the other.[53]

The structures of several large molecules which prove to have high symmetry have recently been established by electron-diffraction studies, notably those of hexamethylenetetramine, phosphorus tri- and pent-oxide, arsenious oxide,[54] phosphorus sulphoxide,[55] and tetranitromethane.[48] The first five of these have structures based on a tetrahedral cage with nitrogen, phosphorus, or arsenic atoms at the four corners and oxygen atoms or methylene groups bridging the six sides. The compounds in the " quinquevalent " states have four more oxygen or sulphur atoms attached outside to the phosphorus atoms. The high degree of symmetry made possible very good determinations of bond lengths in these compounds, some of which will be mentioned in the following sub-section. Tetranitromethane has the nitro-groups arranged in regular tetrahedral fashion; they are symmetrical about the C–N bonds, and vibrate with an amplitude of *ca.* $20°$ about skew mean positions.

Electric moments have proved valuable for confirming the square arrangement of four valencies attributed to the nickel, palladium, platinum, and gold atoms in certain of their complex compounds. This has usually been because the moments enable the *cis*- and *trans*-forms to be differentiated and identified, the former being the more polar of the two. The first example was that of nickel in the glyoximes. Only one form of the *p*-chlorophenyl-*n*-butyl derivative could be isolated : it had a moment nearly the same as that of nickel glyoximes which did not contain polar substituents in the hydrocarbon radicals, and it was therefore presumed to be the *trans*-

[51] I. E. Coop and L. E. Sutton, *J.*, 1938, 1869.

[52] See ref. (i) 33, p. 705.

[53] K. Higasi and S. Uyeo, *Bull. Chem. Soc. Japan*, 1939, **14**, 87.

[54] (*a*) L. R. Maxwell, S. B. Hendricks, and L. S. Deming, *J. Chem. Physics*, 1937, **5**, 626; (*b*) G. C. Hampson and A. J. Stosick, *J. Amer. Chem. Soc.*, 1938, **60**, 1814.

[55] A. J. Stosick, *ibid.*, 1939, **61**, 1130.

form.[56]   Complexes of the type $[NiX_2(PR_3)_2]$ have been isolated in only one form which is apparently *trans* if X = Cl, Br, or I and R = Et, Pr^a, or Bu^a, but *cis* if X = NO_3.[57]   Both *cis*- and *trans*-platino-complexes of formula $[PtX_2Y_2]$ have been isolated, wherein X may be one of several electronegative atoms or groups and Y is an alkyl or aryl cyanide, *iso*cyanide, sulphide, phosphide, arsenide, or antimonide : the isomers have large differences of moment which make their identification easy.[58]   Only the *trans*-forms of the similar pallado-complexes have been isolated.[59]   The observed moments of $[Bu^a_3P)PdCl_2]_2$ and of its arsenic analogue indicate a state of tautomerism between the three possible stereoisomeric structures.[60] *X*-Ray crystallographic determinations of the structures of $[Et_2AuBr]_2$ and of $[Pr^a_2AuCN]_4$ have shown that these molecules are symmetrical.[61]   In common with the *trans*-forms of some of the complexes previously mentioned, they have apparent dipole moments of $1 \cdot 0$—$1 \cdot 5$ D., which can now be attributed to atom polarisation (see p. 62) arising from the large, opposed dipoles which they contain.

Structure.—Considerations of space make it impossible to discuss more than very few of the problems of molecular structure on which light has recently been thrown by electric-moment or electron-diffraction studies; and they compel a very arbitrary choice of subject.   The two selected are (1) the nature of the bonds formed between oxygen and other elements, when the higher valency state of the latter is developed thereby; (2) the cause of the discrepancies between observed and predicted values of the bonds formed by halogens.

(1) *Bonds between oxygen and other elements.*   The success with which the formulæ of many compounds could be systematised if the valency group of electrons were assumed to be an octet [62] led to the general acceptance of electronic formulæ in which octets were ascribed to atoms whenever possible.   This tendency was strengthened by the interpretations of parachor measurements and of some stereochemical observations.[63]   Thus it came about that, in compounds

[56] H. J. Cavell and S. Sugden, *J.*, 1935, 621.

[57] K. A. Jensen, *Z. anorg. Chem.*, 1936, **229**, 265.

[58] (*a*) *Idem, ibid.*, 1935, **225**, 97; (*b*) 1936, **229**, 225; 1937, **231**, 365.

[59] F. G. Mann and D. Purdie, *J.*, 1935, 1549.

[60] *Idem, ibid.*, 1936, 873.

[61] A. Burawoy, C. S. Gibson, G. C. Hampson, and H. M. Powell, *J.*, 1937, 1690.

[62] G. N. Lewis, " Valence and the Structure of Atoms and Molecules," New York, 1923.

[63] (*a*) N. V. Sidgwick, " The Electronic Theory of Valency," Oxford, 1927; (*b*) S. Sugden, " Parachor and Valency," London, 1930.

where the valency of an atom has been developed to one of its higher states by combination with oxygen, the bond attaching the additional oxygen atom was presumed to be a co-ordinate link, and not a double bond as in earlier valency theory. Phosphoryl compounds were written as $X_3P \rightarrow O$, thionyl and sulphuryl ones $X_2S \rightarrow O$

$$O\leftarrow \overset{\overset{O}{\uparrow}}{Cl}-O-\overset{\overset{O}{\uparrow}}{Cl}\rightarrow O$$
$$\underset{O}{\downarrow} \qquad \underset{O}{\downarrow}$$
(I.)

and $X_2S\overset{\nearrow O}{\underset{\searrow O}{}}$, and chlorine heptoxide as (I), corresponding structures being ascribed to related compounds, including the oxy-acids and their ions. As newer physical methods were applied, the validity of these formulations became less certain.

The first clear challenge came when, on the basis of their " adjacent charge rule," L. Pauling and L. O. Brockway [64] suggested that the octet formulations of several oxy-acids must be wrong, and that actually there is resonance between several possible structures with double bonds holding one or more of the oxygen atoms. They supported their argument by pointing out that the bond lengths in the common oxy-acid ions, determined by X-ray examination of crystals, are much less than those to be expected for single bonds. Either, therefore, co-ordinate links must be shorter than normal single bonds, or the bonds in question cannot be co-ordinate links.
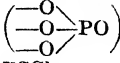
Electron-diffraction studies soon provided further examples of anomalous " co-ordinate " links, and also, together with X-ray crystal-structure data, demonstrated that the true co-ordinate link has the same length as a normal bond,[65] in agreement with a theoretical prediction.[66] This was shown particularly clearly in trimethylamine oxide,[65(b)] where, since the donor atom is of the first short period, its covalency is limited to four; so the fourth atom, the oxygen, can only be held by a co-ordinate link. The $N \rightarrow O$ bond length is 1·36 A.; the sum of the single-bond covalent radii is also 1·36 A. In contrast to this, the bonds with oxygen formed by elements in later periods, which are not restricted to quadricovalency, are sometimes as short as or even shorter than triple bonds, as may be seen from the following table, which supplements the earlier data for oxy-acid ions.

Electric dipole-moment data emphasise the difference still further. The moment for a co-ordinate link 1·36 A. long, if an electron were completely transferred, would be 6·43 D. In actual fact the $N \rightarrow O$ link is not quite so polar : recent measurements on amine oxides

[64] J. Amer. Chem. Soc., 1937, **59**, 13.

[65] See (a) K. J. Palmer and N. Elliott, ibid., 1938, **60**, 1852; (b) M. W. Lister and L. E. Sutton, Trans. Faraday Soc., 1939, **35**, 495.

[66] N. Elliott, J. Amer. Chem. Soc., 1937, **59**, 1380.

Distance, A.

Link.	Compound.	$l_{obs.,}$ A.	$l_{calc.,}$ single.	double.	triple.
N→O	NOMe$_3$	1.36 ± 0.03 [65(b)]	1.36	1.18	—
SO	SO$_2$Me$_2$	1.44 ± 0.03 [65(b)]	1.70	1.52	1.47
,,	SO$_2$	1.43 ± 0.01 [67]	,,	,,	,,
,,	SO$_3$	1.43 ± 0.02 [21]	,,	,,	,,
,,	SO$_2$Cl$_2$	1.43 ± 0.02 [21]	,,	,,	,,
,,	SO$_2$F$_2$	1.43 ± 0.02 [68]	,,	,,	,,
PO	POF$_3$, POF$_2$Cl, POFCl$_2$, POCl$_3$	1.55 ± 0.03 [42]	1.76	1.57	1.44
,,	$\left(\begin{smallmatrix}-O\\ -O\\ -O\end{smallmatrix}\!\!>\!PO\right)_4$	1.39 ± 0.02 [54(b)]	,,	,,	,,
PS	PSCl$_3$	1.94 ± 0.03 [43]	2.14	1.95	1.81
,,	PSF$_3$	1.85 ± 0.02 [68]	,,	,,	,,

show that it is approximately 4·38 D.[69] But the SO, PO, and PS bonds which should be more polar (6·86—9·31), even shortened as they are, are actually much less so. The most recently calculated values are 2·0—2·5, 3·5, and 2·5 D., respectively.[70, 71]

There is but one step lacking to make the proof complete; this is to show that when sulphur or phosphorus does form genuine co-ordinate links a highly polar bond is generated. This has now been done by measuring the moments of complexes between trimethyl-amine, trimethylphosphine, diethyl ether, diethyl sulphide, and boron trichloride or trifluoride.[71] It is impossible for the boron compound to combine save by accepting a co-ordinate link from the nitrogen, phosphorus, oxygen, or sulphide atoms. In all cases there is a large difference between the moment of the complex and the sum of those of the uncombined constituents. The abrupt drop in the difference which occurs from nitrogen to phosphorus compounds when an oxygen atom is attached is not observed in these complexes. Hence there can be little doubt that the bonds from phosphorus or sulphur to oxygen are not of the same type as those to boron, *i.e.*, they are *not* co-ordinate links.

The extreme shortness has been explained as the result of resonance with triple-bonded structure, *e.g.*, S≦O; but a large contribution, such as is essential on this theory in most of the oxy-compounds examined, would reduce the moment of the SO and PO bond to zero, or even reverse it. No such drastic effect is actually

[67] V. Schomaker and D. P. Stevenson, *J. Amer. Chem. Soc.*, 1940, **62**, 1270.

[68] D. P. Stevenson and H. Russell, *ibid.*, p. 3264.

[69] E. P. Linton, *ibid.*, p. 1945; these measurements agree reasonably well with unpublished observations made by J. S. Hunter and N. J. Leonard at Oxford.

[70] I. E. Coop and L. E. Sutton, *Trans. Faraday Soc.*, 1939, **34**, 505.

[71] Unpublished observations by G. M. Phillips at Oxford.

observed : the bond is still decidedly polar, and the negative pole is towards the oxygen. It has therefore been suggested that the SO, PO, and PS bonds are really double bonds, but that the ordinary radii do not apply.[70] These are stable bonds, with large heats of formation; and it is possible that they therefore involve bonding orbitals of a different kind from those which would correspond to the covalent radii used. The change of bond is thus attributed to a change in bonding orbitals, but to one which does not affect the multiplicity of the bond. Such changes have already been postulated occasionally, e.g., to explain the difference between the ter- and quadri-covalent radii for boron; [72] and it now appears possible that they may frequently be responsible for changes of bond-length which have hitherto been attributed to change in multiplicity.

(2) *Halogen bonds.* Halogen compounds are frequently covalent and conveniently volatile. Many have therefore had their structure determined from the electron-diffraction patterns. It has been found that, although the lengths of the halogen bonds are usually equal to the sum of the appropriate radii in saturated organic compounds, they are frequently different from it in unsaturated ones, or in inorganic ones.

The organic compounds have been extensively discussed in a previous Report.[73] The general conclusions were that the chloro-, bromo-, and iodo-derivatives of saturated hydrocarbons show no abnormalities in bond lengths, but that the fluorine compounds have short C–F links if there are two or more fluorine atoms on one carbon atom. Chloro-, bromo-, and iodo-derivatives of unsaturated hydrocarbons with the halogen attached to an unsaturated carbon atom also have short carbon–halogen bonds. Later work has shown that the acetylenic derivatives are more abnormal than the ethylenic ones which are affected to much the same degree as the benzenoid ones.[37(e, g)] The only unsaturated fluorine derivative so far examined is fluorobenzene,[74] in which the C–F bond ($l_{\rm CF} = 1\cdot34 \pm 0\cdot04$ a.) is reported to be shortened to about the same extent as are those in carbon tetrafluoride.[75] These facts have been interpreted to mean that there is resonance between the ordinary structure and others in which two unshared electrons of the halogen atom form a double bond with the carbon atom.

Essentially the same explanation had previously been offered for the reductions in the electric moments of unsaturated halogen

[72] H. A. Lèvy and L. O. Brockway, *J. Amer. Chem. Soc.*, 1937, **59**, 2085; see also ref. (i) 35, p. 160.

[73] See refs. (i) 1 and (i) 2.

[74] H. Osaha, *Bull. Chem. Soc. Japan*, 1940, **15**, 31.

[75] See ref. (i) 2.

compounds compared with those of saturated ones ; [37(b)] and there is fair quantitative agreement in the conclusions from the two sets of data about the relative importance of double-bonded structures in chloro-, bromo-, and iodo-compounds.[37(f)] Objections have been raised against this explanation,[76] however, on the grounds that such donation, by going counter to the normal tendency of the halogen to attract electrons and so destabilising the double-bonded structure, should reduce its importance as a component structure in the resonance hybrid. This effect should be particularly marked for fluorine and least for iodine; and it is a most striking fact that, judging from the chemistry of its compounds, fluorine differs from the other halogens in showing no inclination whatsoever to form more than one single bond. Yet although there is some tendency for the changes in length or moment to increase in the order $Cl < Br < I$ it is not very marked, and they certainly do not vanish in fluorine compounds. If, therefore, fluorine forms a double bond it must be that this has a greater heat of formation than two single bonds, just as that of $N{=}N$ is greater than $2(N–N)$.[80] It has been suggested alternatively that there is no double-bonding, but that there is some electrostatic effect which is as yet imperfectly understood.[77] The facts are that when halogens are attached to unsaturated carbon atoms the C–Hal link is shortened, and that, as judged from both electric moment data and chemical behaviour, electrons appear to move from the direction of the halogen atom into the body of the unsaturated system. Although no complete and entirely acceptable explanation seems yet to have been given, it seems on the whole probable that resonance with double-bonded structures is the main cause in the chlorine, bromine, and iodine compounds, but that some other cause may be predominant in the fluorine compounds.

The inorganic compounds have not been systematically discussed in a Report, but the salient points may be briefly summarised as follows. In the halogen derivatives of saturated carbon compounds, with the exceptions previously noted, the halide bond lengths are normal; but in the compounds of most other elements they are abnormal. The N–Cl,[(i) 23] O–Cl, O–F,[35, (i) 14] F–F [78] or S–Br,[79] bonds are too long ; the bonds between halogens and boron or any elements, save the halogens themselves, in the second short period or later periods are in some degree shortened.[80, 81] The fact that there is

[76] See ref. (i) 1.

[77] G. Baddeley, G. M. Bennett, S. Glasstone, and B. Jones, *J.*, 1935, 1827.

[78] L. O. Brockway, *J. Amer. Chem. Soc.*, 1938, **60**, 1348.

[79] D. P. Stevenson and R. A. Corey, *ibid.*, 1940, **62**, 2477.

[80] See ref. (i) 35, Chap. VII.

[81] See A. H. Gregg, G. C. Hampson, G. I. Jenkins, P. L. F. Jones, and L. E. Sutton, *Trans. Faraday Soc.*, 1937, **33**, 852.

contraction only if the central atom belongs to a later period than the first, *e.g.*, silicon, or has an incomplete octet when exercising its normal covalency, *e.g.*, boron, led to the theory that the contractions are all due to resonance with double-bonded structures in which the octet is completed or, in the heavier elements, exceeded.   It would then be expected (cf. p. 77) that the contractions would increase in the order $F<Cl<Br<I$, although this might be opposed by the possibly greater tendency of the lighter halogens, like other light elements, to form double bonds.   In actual fact, the halides of the elements which have incomplete octets in their normal valency state show much the same percentage contraction in chlorides, bromides, and iodides, although the fluoride is considerably shorter; but those of the other elements show a marked *decrease* in contraction, *i.e.*, in abnormality, from fluoride to iodide.   This suggests that there may be two causes of contraction,[81, 82] the double-bonding, postulated above, which operates in the first class of halide, and another, so far not understood, which certainly operates in the second class and possibly in both.   The decrease of contractions in the order $F>Cl>Br>I$ and the existence of expansions in the N–Cl, O–Cl, S–Br, O–F, and F–F bonds suggest that there is a qualitative relation between the strength and the length of a bond, and since the " electronegativity co-ordinates " in Pauling's electronegativity map [83] are derived from bond energies, this may be expressed by saying that large differences in electronegativity tend to make the bond short, whereas small ones tend to make it long.   This condition alone is not sufficient, and consequently it has been regarded rather as permissive.[80]   If double-bonding can occur when the bonds are highly polar, then there is contraction.   No explanation of the expansions is provided on this theory, however.   This lack and the objections to any double-bonding mechanism make it desirable to look for possible alternatives; and the following is worthy of consideration.   The shortening or lengthening of halide bonds may be connected with variations in the bonding orbitals used by the halogen and the central atom, these being of a kind which does not affect the multiplicity.   If a large heat of bond formation can promote hybridisation of atomic orbitals to give new bonding orbitals, it may give rise to new and smaller covalent radii, whereas a low heat of formation, by discouraging such hybridisation, may increase the radii.   When fluorine combines with itself or oxygen, oxygen with fluorine or chlorine, sulphur with bromine, or nitrogen with chlorine, it is possible that the bonding orbitals are largely derived

[82] A table of percentage contractions, including new results, will appear in a forthcoming paper by M. W. Lister and L. E. Sutton.

[83] See ref. (i) 35, Chap. II.

from atomic p orbitals ; but when these atoms combine with other elements to form stronger bonds they use sp hybrid orbitals.   Since the latter bonds are the commoner, they give rise to the smaller " standard " covalent radii.*   Furthermore, while carbon can only use sp^3 hybrid bonding orbitals, silicon could possibly use hybrids involving d orbitals as well in a strong bond such as the Si–F bond; and these strong bonding orbitals might correspond to considerably reduced radii.   Thus the conditions which permit double-bonding also permit this change in hybridisation.

One further general rule, that contractions diminish with increasing weight of the central atom when it is attached to the same halogen, may be explained on the grounds that the effect of changes in the valency shell has steadily less effect upon the electronic arrangements of the atom as a whole with increase of atomic number of the latter.

It will be noticed that this suggestion unifies not only the contractions and the extensions of halide bonds, but also the contractions of the oxide bonds in the higher oxides and oxy-acids, which were discussed previously.   This is an attractive feature, but until the idea has been developed beyond its present crude, incomplete, and qualitative form its real value can hardly be judged.

<div style="text-align:right">L. E. S.</div>

4. KINETICS.

Photochemistry.

Primary Processes.—In the previous Report on Photochemistry,[1] it was pointed out that a photo-activated molecule may react in several ways at comparable rates, the procedure favoured being determined by a variety of factors.   In the last few years, a number of extensive investigations, more particularly of organic molecules, has facilitated a more complete recognition of these processes in relation to the absorption spectra; it has become clear, however, that the characteristics of the absorption spectrum alone are no certain assurance of the type of process occurring.

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[1] *Ann. Reports*, 1937, **34**, 54.

* (Added in proof, 25/2/41.)   V. Schomaker and D. P. Stevenson (*J. Amer. Chem. Soc.*, 1941, **63**, 37) suggest increases of the standard covalent radii for oxygen, nitrogen, and fluorine and give an empirical relation between bond length and difference of electronegativity values.[83]   The hypothesis that electronegativity difference alone is sufficient to cause contraction was abandoned some time ago as inadequate.   Moreover, the uncertainty of the significance of electronegativity values [ref. (i) 6] makes it necessary to consider what other factors which may strengthen the bond will also shorten it, as is done here.

In general, absorption of a light quantum by a molecule may result in the production of one of several excited states. When energy is absorbed at a particular bond by a process of transition to a repulsive energy level or to a sufficiently high point on an attractive level, rupture of the bond results within one vibration period. M. Burton and G. K. Rollefson [2] define a simple rupture process as one in which, on the average, decomposition occurs at the locus of absorption in less than one vibration period after the creation of the excited state; on the other hand, if, during the lifetime of the excited state, some shift of energy or position within the molecule occurs from the initial excited state so that rupture finally takes place, either at some other bond or at the initially absorbing bond, we deal with a predissociation process, appearing in the spectrum in the form of the well-known diffuse absorption bands. Such predissociation may then be divided into two classes, spontaneous and induced, and a distinction made by considering the effect of altered pressure, but in general it is difficult to determine exactly the actual process involved. Unambiguous interpretations of such principles are usually confined to the relatively simple case of the diatomic molecule. In sulphur, S_2, for example,[3] the absorption bands in the region 2435—2615 A. are blurred even at low pressure, and a spontaneous predissociation is hence concerned. The absorption spectrum at 2615—2799 A. is sharp at low pressures, but becomes blurred at higher pressures; the previously forbidden transition is now made possible by the fields introduced by neighbouring molecules. In iodine, relatively few iodine atoms are produced in the discrete region of the spectrum, but the yield is greatly increased when a magnetic field is applied or the pressure is increased by the addition of otherwise inert gas molecules. In other words, the discrete spectrum is here associated with an induced predissociation.

In polyatomic molecules, where the term vibration period itself cannot be so exactly defined, the properties of hypersurfaces corresponding to different energy levels may be considered, the intersection of surfaces being comparable to the intersection of lines in the potential-energy diagram for a diatomic system. Decomposition may in simple cases occur as before as a result of absorption from the normal state to a repulsive or weakly attractive surface, in which case a continuum would be observed in the spectrum. Similarly, other concepts derived from the study of diatomic systems may be applied directly to the polyatomic ones. In complex molecules, however, the spectral characteristics generally are not

[2] *J. Chem. Physics*, 1938, **6**, 416.
[3] Cf. G. Herzberg and L. G. Mundie, *ibid.*, 1940, **8**, 263.

so clear.   Diffuseness, for example, is not always sufficient in deciding between a spontaneous and an induced process.   R. G. W. Norrish,[4] in a discussion of the relationship of fluorescence to photolysis in gaseous systems, has pointed out that the equation $\tau \Delta \nu \sim 1$, connecting the breadth of an absorption line ($\Delta \nu$) and the life-time (τ) of the excited molecule, indicates that at 3000 A. a reduction of the life-time from 10^{-8} sec., the normal life-time of the fluorescing molecule, to 10^{-13} sec., corresponds to an increase in the natural breadth of the line by a factor of 10^5; the previously sharp lines become diffuse, and the onset of diffuseness in this case corresponds closely to the photolytic threshold.   In a diatomic molecule, there may be thus a sharp demarcation between fluorescence and pre-dissociation as shown by the spectrum.   On the other hand, in a polyatomic molecule, the life-period may be much longer by reason of the complexity of the vibration; if τ be now 10^{-10} sec. instead of 10^{-13} sec., the natural breadth of the line at 3000 A. is only 10^{-2} instead of 10 A.   Diffuseness is not now apparent, yet the probability of decomposition is 100 times (*i.e.*, $10^{-8}/10^{-10}$) that of fluorescence. Under these conditions the efficiency of photolysis may then be nearly unity, fluorescence being almost entirely absent, and yet sharp rotational structure is to be observed in the spectrum.   Disappearance of fluorescence is then on this basis a better criterion of predissociation than diffuseness.

Care must therefore be taken in extending the spectral interpretations applicable in the case of simple molecules to those of greater complexity, and in particular, relatively greater attention must be paid to the nature and amounts of the products of photolysis for the given conditions of wave-length and temperature.   In this respect the simpler aldehydes and ketones have again been the subjects of much investigation.   Absorption here occurs at the CO link, but rupture never follows at this point; predissociation processes are therefore involved.   The main problem is then the determination of the relative importance of the three primary reactions :

$$COR_1R_2 \longrightarrow R_1R_2 + CO \ ; \ \ COR_1R_2 \longrightarrow R_1 + COR_2 \ ;$$
$$COR_1R_2 \longrightarrow R_1 + R_2 + CO$$
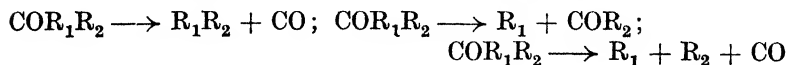
With formaldehyde, a fine-line absorption has been reported for the region 3570—2750 A., followed by a diffuse region 2750—2500 A., and a continuous background from approximately 2670 A. to lower wave-lengths.   The products of photolysis are almost entirely hydrogen and carbon monoxide; even in the Schumann region

[4] *Trans. Faraday Soc.*, 1939, **35**, 21 ; for a general discussion of fluorescence and photochemical kinetics in polyatomic molecules, see W. A. Noyes, junr., and F. C. Henriques, junr., *J. Chem. Physics*, 1939, **7**, 767.

there is no evidence of CH_2 radicals or oxygen atoms.[5] Fluorescence
has been observed at 3530, 3400, and 3270 A., indicating a life-period
for the excited molecule of 10^{-8} to 10^{-7} sec. Addition of air to
100 mm. pressure does not diminish the fluorescence appreciably; [6]
this predissociation process must then be spontaneous in this spectral
region. The sharp-line spectrum might then indicate that, while
the molecules may remain in a stable hypersurface for some time
before decomposing in that surface, a transition from that surface
to another is forbidden. The decomposition reaction would then
be best represented [2] by

$$H \cdot CHO^* \longrightarrow H_2 + CO \quad . \quad . \quad . \quad . \quad (a)$$
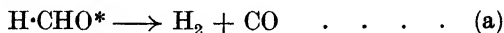
By experiments involving the use of iodine vapour to remove any
hydrogen atoms formed, E. Gorin [7] finds, however, that at 3130 A.
as well as at 2537 A., the permanent-gas product is almost exclusively
carbon monoxide, the HI/CO ratio being nearly 2 at these wave-
lengths; the main reaction is on this basis

$$H \cdot CHO \longrightarrow H + CHO \quad . \quad . \quad . \quad . \quad (b)$$

At 3650 A., a considerable quantity of hydrogen is formed and the
data here indicate that the probability of reaction (a) to that of
reaction (b) at the temperature concerned (100°) is 0·3 to 0·7.
Such results serve to emphasise the difficulty of determining the
exact process of decomposition occurring in such complex molecules
from examination of the spectra alone; diffuseness does not neces-
sarily indicate a spontaneous process, while discrete absorption
may be associated with an induced or spontaneous process.

Gorin deduces [7] from his results that the heat of dissociation
for the first hydrogen atom in formaldehyde is considerably smaller
than that formerly recognised. From the predissociation limit,
which, however, can only give an upper limit, approximating to
the true value the more complex the molecule (see ref. 2), R. Mecke [8]
deduced the value of 102 kg.-cals.; the wave-length 3650 A. (above)
corresponds to an energy of 78 kg.-cals. The stability of the formyl
radical has been previously noted: [9] according to the above, 26
kg.-cals. are required to dissociate it. It is to be pointed out that,
according to E. Bergmann and R. Samuel,[10] in certain cases two bonds

[5] R. G. W. Norrish and W. A. Noyes, junr., *Proc. Roy. Soc.*, 1937, *A*, **163**,
221.

[6] G. Herzberg and K. Franz, *Z. Physik*, 1932, **76**, 720; cf. G. H. Dieke and
G. B. Kistiakowsky, *Proc. Nat. Acad. Sci.*, 1932, **18**, 367.

[7] *J. Chem. Physics*, 1939, **7**, 256.

[8] *Z. Elektrochem.*, 1930, **36**, 589.

[9] F. Patat, *Z. physikal. Chem.*, 1936, *B*, **32**, 274; M. Burton, *J. Amer.
Chem. Soc.*, 1938, **60**, 212.

[10] *Nature*, 1938, **141**, 832.

of an absorbing molecule may be broken simultaneously without involving two single-bond energies, by the direct transition from the ground state to a repulsive term, correlated to a saturated molecule of lower valency. It is not always clear from present experimental evidence how the energy of one particular bond appears in relation to the energy required in the photodecomposition.

At 2537 A., the primary process

$$H \cdot CHO \longrightarrow H + H + CO \quad . \quad . \quad . \quad . \quad (c)$$

becomes energetically possible, but in presence of iodine the yield of hydrogen iodide would be double that expected from reaction (b). There is, however, no significant change [7] in the values at 2537 as compared with those at 3130 A., and it is thus to be concluded that reaction (c) does not play any important part in the formaldehyde photolysis.

In acetaldehyde, the discrete absorption spectrum extends from 3484 to 3050 A., where the diffuse spectrum begins. A continuum underlies the whole. On the formaldehyde analogy, we may have two predissociation processes in action simultaneously, one referring to the production of free radicals and the other giving directly methane and carbon monoxide. One cannot assume, however, that the production of free radicals will in all cases be favoured by decrease in wave-length. Experiments to determine which process is favoured by given conditions have been carried out [11] on the basis that free radicals catalyse the chain thermal decomposition of acetaldehyde; at high temperatures the chain length increases rapidly and accounts for practically all the decomposition. At high temperatures, therefore, determination of the ratio of quantum yields for two wave-lengths gives the ratio of concentrations of free radicals at these wave-lengths. It has thus been concluded that, at room temperature, more radicals are produced at 2652 A. than at 3132 A.; but as the temperature is raised, the yield of radicals at 3132 A. relatively increases, and at 100° the yields are equal. Fluorescence fades correspondingly as the temperature is raised, this being in agreement with the view that at 3132 A. the dissociation is aided by thermally excited vibrational energy. The processes concerned may be analysed by the principles already cited. On the basis of only one excited state from which the molecule may dissociate, there may be a slow decomposition in the same hypersurface into ultimate molecules, this occurring when the increase in energy is not sufficient to break the C–C bond to give free radicals. If a sufficient energy is absorbed, transition from the initially excited state to a weakly attractive

[11] G. K. Rollefson and D. C. Grahame, *J. Chem. Physics*, 1939, **7**, 775.

state will lead to such dissociation.   G. K. Rollefson and M. Burton have shown, however,[12] that under these conditions the probability of free-radical production is highest when the amount of energy contained by the molecule in the excited state is a minimum in excess of that required to cause free-radical decomposition; thus, rise in temperature decreases the free radical yield at 2652 A. and increases it at 3132 A.   Further, at still shorter wave-lengths, e.g., 2536 A., free-radical production ought to be less than at 2652 A. E. Gorin,[7, 13] in fact, finds from the photodecomposition in presence of iodine at 100° that the two primary reactions occur simultaneously, but at 2536 A. dissociation into molecules is favoured, the ratio being 2·9 : 1.   At 3130 A. the free-radical mechanism is 2·6 times as probable as the decomposition into ultimate molecules.   Further confirmation of such trends has been obtained by tellurium mirror removal methods.[14]   Fluorescence   in   acetaldehyde   has   been ascribed to the combination of acetyl radicals to give diacetyl; [15] that only a very faint fluorescence has been observed at 2652 A.[16] is not thus in disagreement with this view.   It is noteworthy that the green fluorescence of acetone illuminated by light of 3130 A., identical with that found in diacetyl itself excited by wave-lengths 3650, 4047, and 4358 A., appears only after continued radiation and is therefore to be attributed to the diacetyl formed; [17] since diacetyl does not itself fluoresce appreciably when irradiated with 3130 A. unless acetone is present, the simplest picture is that excitation arises by some collision of the second kind.

F. E. Blacet and D. Volman [18] find that the volatile products of decomposition of acetaldehyde over the range 3340—2380 A. are solely methane, hydrogen, and carbon monoxide, the ratio H_2/CO increasing as the wave-length is decreased.   Discussion is given, for room-temperature photolysis, of a series of reactions based on the free-radical mechanism similar to that proposed for high-temperature photolysis [19] and to that advanced for the thermal decomposition.[20]   This chain mechanism allows explanation of the altered ratio H_2/CO with change in pressure, light intensity, and

[12] J. Chem. Physics, 1938, 6, 674.

[13] Acta Physicochim. U.R.S.S., 1938, 9, 681.

[14] P. A. Leighton and D. Volman, J. Chem. Physics, 1939, 7, 781.

[15] W. A. Noyes, junr., and F. C. Henriques, junr., J. Chem. Physics, 1939, 7, 767; see G. M. Almy, H. Q. Fuller, and G. D. Kinzer, ibid., 1940, 8, 37.

[16] D. C. Grahame and G. K. Rollefson, ibid., p. 98.

[17] G. M. Almy and S. Anderson, ibid., p. 805.

[18] J. Amer. Chem. Soc., 1938, 60, 1243.

[19] J. A. Leermakers, ibid., 1934, 56, 1537; D. C. Grahame and G. K. Rollefson, J. Chem. Physics, 1940, 8, 98.

[20] F. O. Rice and K. F. Herzfeld, J. Amer. Chem. Soc., 1934, 56, 284.

temperature. It is possible that the effect of altered wave-length is partly connected with the excess energy remaining in the CHO radical after the primary dissociation. Further information regarding polymerisation processes involving CHO and CH_3 is desirable. No polymerisation was found in presence of iodine,[7] indicating free radicals as the cause of polymerisation; the smaller polymerisation observed normally at low wave-lengths is in agreement with the effects of altered wave-lengths illustrated above. The decomposition of acetaldehyde, both photochemical and thermal, has been discussed in detail in a number of papers; [21] it is concluded that the C–C bond strength is of the order 75 kg.-cals. The photolysis of acetyl bromide has been investigated and discussed [22] on the basis of three primary steps, two yielding free radicals and the third involving direct decomposition of the activated molecule into the final products.

V. R. Ells and W. A. Noyes, junr.,[23] conclude that methyl ethyl ketone at 25° dissociates mainly to give ethyl radicals in the near ultra-violet (3000 A.) but at shorter wave-lengths (1880—2000 A.) methyl and ethyl radicals are produced in nearly equal amounts from the primary process. The quantum yield of carbon monoxide formation from diethyl ketone is approximately unity in both wave-length regions. In higher aldehydes and ketones a further type of decomposition has been previously noted, e.g.,

$$CH_3 \cdot CH_2 \cdot CH_2 \cdot CHO \longrightarrow CH_3 \cdot CHO + C_2H_4 \qquad . \quad . \quad . \quad (d)$$
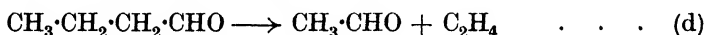
From its probability to that of other reactions this may be interpreted as an induced predissociation process.[2] E. Gorin [7] has concluded that in methyl ethyl ketone vapour at 70° the primary quantum efficiency in the decomposition into free radicals is of the order unity, and thus suggests that the type (d) reaction may in this case occur by secondary processes involving interaction between these radicals. Against this, it is to be pointed out that C. H. Bamford and R. G. W. Norrish [24] find the production of molecules according to type (d) mechanism to occur in paraffinoid solution as readily at room temperature as at 100°, whereas decomposition yielding free radicals is completely suppressed in ketone photolysis at room temperature, this being ascribed to recombination of radicals by the principle of primary recombination following restraint by a shell of solvent molecules. Only at temperatures of 70—100°

[11] M. Burton, J. Chem. Physics, 1939, 7, 1072; T. W. Davis and M. Burton, ibid., p. 1075; M. Burton, H. A. Taylor, and T. W. Davis, ibid., p. 1080; H. A. Taylor and M. Burton, ibid., p. 414; F. O. Rice and W. R. Johnstone, J. Amer. Chem. Soc., 1934, 56, 214.

[22] D. H. Etzler and G. K. Rollefson, ibid., 1939, 61, 800.

[23] Ibid., p. 2492.   [24] J., 1933, 1531, 1544.

do the free radicals show hydrogenation at the expense of the solvent, which thus shows equivalent unsaturation. It is difficult to assess possible effects of solvent on the relative rates of the two possible decompositions from the point of view of induced predissociation, and it may be argued that direct comparison between solution and gas phase is here not justifiable. It is, for example, possible that the free-radical mechanism, involving a different hypersurface from that of the ultimate molecule formation, is suppressed at low temperatures in a process which produces no free radicals, in which case application of the primary recombination principle would be unnecessary. Comparison of reactions in the gas phase with those in solution has been given by R. G. Dickinson; [25] there are, however, few other recent investigations from this point of view.

Reference has been made in previous Reports to various methods (e.g., use of metallic mirrors or of nitric oxide) of confirming and identifying free radicals in general. Primary and secondary aliphatic amines yield hydrogen atoms and alkylamino- or dialkyl-amino-radicals respectively in the primary act, the hydrogen atoms being detected by their reaction with propylene.[26] Irradiation of hydrazine in the presence of propylene confirms similarly the production of atomic hydrogen in the initial decomposition for wave-lengths of ca. 2200 A., and nitric oxide may be used to detect N_2H_3 radicals in this photolysis as well as the NH_2 radicals produced in the photolysis of ammonia.[27] The addition of nitric oxide assists the photodecomposition of methyl iodide [28] by removal of methyl radicals involved in the reverse reaction.

A variety of photochemical methods have thus been employed in producing free radicals in order to study their subsequent reactions, e.g., photolysis of methyl ethyl ketone,[29] of such compounds as diethyl-mercury and -zinc,[30] dimethylmercury,[31] of alkyl iodides,[32] of alkyl iodides in the presence of mercury to remove iodine atoms,[33] and by the mercury-sensitised production of hydrogen atoms in the presence of olefins.[34] Methyl radicals are thus found to be more

[25] J. Physical Chem., 1938, 42, 739.
[26] C. H. Bamford, J., 1939, 17; cf. dimethyl- and diethyl-nitrosoamines, idem, ibid., p. 12.
[27] Idem, Trans. Faraday Soc., 1939, 35, 568.
[28] T. Iredale, ibid., p. 458.
[29] W. J. Moore, junr., and H. S. Taylor, J. Chem. Physics, 1940, 8, 466.
[30] Idem, ibid., p. 396.
[31] J. P. Cunningham and H. S. Taylor, ibid., 1938, 6, 359.
[32] W. West and L. Schlessinger, J. Amer. Chem. Soc., 1938, 60, 961.
[33] J. C. Jungers and L. M. Yeddanapalli, Trans. Faraday Soc., 1940, 36, 483.
[34] W. J. Moore, junr., and H. S. Taylor, J. Chem. Physics, 1940, 8, 504.

effective than ethyl radicals in polymerising ethylene,[29] in accordance with other results; disappearance of the radicals in this polymerisation is accounted for [33] by saturation by hydrogen-atom capture and by mutual recombination. Detailed discussion of reactions of methyl radicals has been given by H. A. Taylor and M. Burton.[35] In the case of the metallic alkyls, further products may arise by interaction of radicals with the alkyl molecules themselves.[31] Further check on the actual concentrations of such radicals is desirable.

Primary Quantum Efficiencies.—The overall photochemical yields in the above-mentioned organic molecule decompositions are as a rule less than unity, and there are two ways in which such low values may be explained. In the first, the primary quantum efficiency may be unity but the secondary reactions, *e.g.*, recombination of the radicals initially produced, may reduce the overall yield. Alternatively, the efficiency of the primary reaction, chemically speaking, may not be unity, by reason of fluorescence, collisional deactivation, or internal degradation of energy. It might be expected that in more complex molecules, with their greater possibilities for internal degradation, the low quantum efficiencies might be ascribed to this cause.[36] Some recent investigations, however, allow of measurement of the primary quantum efficiencies apart from the overall yield; the methods of attack on the problem and the results obtained are of considerable interest.

In aldehyde and ketone photolysis, E. Gorin [7] employed iodine vapour to remove as alkyl iodides or hydrogen iodide the radicals primarily formed, the method depending on the fact that the saturated hydrocarbons that may be formed by direct splitting of the aldehyde and ketone do not react with iodine in the temperature range investigated. Analysis of the reaction products then distinguishes quantitatively primary reactions giving free radicals from those giving saturated hydrocarbons. The principle of the method may be exemplified by acetone. Here the overall quantum yield for given conditions of temperature, wave-length, light intensity, and pressure is known. A series of experiments with and without iodine vapour is carried out. The ratio of carbon monoxide molecules in absence of iodine to methyl iodide molecules, multiplied by the known overall quantum yield in the absence of iodine, gives the quantum efficiency of the primary stage. With acetone, Gorin finds the quantum efficiency of the formation of methyl iodide to be approximately unity, in the unfiltered light of the mercury arc. The primary process must then be

$$CH_3 \cdot CO \cdot CH_3 \longrightarrow CH_3 + CH_3 \cdot CO$$
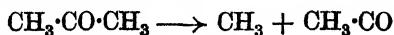
[35] *J. Chem. Physics*, 1939, **7**, 675.
[36] See R. G. W. Norrish, *Trans. Faraday Soc.*, 1939, **35**, 22.

with an efficiency of unity. In the presence of iodine, only a small amount of carbon monoxide is formed below 80°, this confirming the stability of the acetyl radical; the low overall yield in absence of iodine is then to be ascribed to the recombination of methyl and acetyl radicals.

In acetaldehyde, as discussed previously, at 3130 A. and 100°, dissociation into free radicals is 2·6 times as probable as that into molecules. The sum of the quantum yields for both reactions was found to be unity. The normal low overall quantum yield must then be due to recombination of the radicals CH_3 and CHO. In formaldehyde, the primary process at 3130 A. is dissociation into free radicals, and the quantum efficiency of hydrogen iodide formation is of the order unity, this again indicating unit efficiency for the primary stage.

E. Gorin finds the decomposition scheme for methyl ethyl ketone to be somewhat similar to that of acetone; in the presence of iodine, the amount of carbon monoxide is relatively very small when compared with the amount of alkyl iodide. The principal primary reactions are thus :

$$C_2H_5 \cdot CO \cdot CH_3 \longrightarrow C_2H_5 + CH_3 \cdot CO$$

and $\qquad C_2H_5 \cdot CO \cdot CH_3 \longrightarrow CH_3 + C_2H_5 \cdot CO$
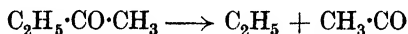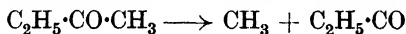
there being other evidence [37] to show that these have approximately equal probabilities; propane is formed in small amount only (5%) by the primary process

$$C_2H_5 \cdot CO \cdot CH_3 \longrightarrow C_3H_8 + CO$$
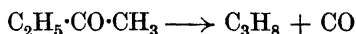
Comparison of photolysis rates for $CH_3 \cdot CO \cdot C_2H_5$ and $CH_3 \cdot CO \cdot CH_3$ in the presence of iodine, corrected for different absorption coefficients, indicates also that the primary dissociation here has a quantum efficiency of about unity.

It is thus to be observed that illumination of these organic molecules in the presence of iodine vapour leads generally to dissociation with a primary quantum efficiency of order unity. In some apparently simpler molecules, however, such unit efficiency is not observed. The photolysis of ammonia may be here considered. The kinetics of this decomposition have already been the subject of considerable experiment and discussion.[38] The main difficulty is the explanation of the low overall quantum yield, the predissociation spectrum and the absence of fluorescence being taken as indicating the dissociation of the molecule in 10^{-13} sec. after

[37] R. G. W. Norrish and (Miss) M. E. S. Appleyard, *J.*, 1934, 874; see also ref. (23).

[38] See, *e.g.*, H. S. Taylor, *J. Physical Chem.*, 1938, **42**, 783.

absorption of the quantum. Since the decomposition is repressed by the addition of atomic hydrogen,[39] it was first assumed that ammonia is partly re-formed by combination of the hydrogen atoms and NH_2 radicals initially produced by absorption, while hydrogen is formed by hydrogen-atom recombination on the walls of the vessel or in the gas phase. Actual measurement of the hydrogen-atom concentration by the para-hydrogen conversion method [40] gave, however, a value much lower than that expected on the above basis. Since hydrazine is formed in small amounts in the photolysis and is known to react with atomic hydrogen, it was suggested [41] that the low atom concentration in the ammonia photolysis was due to reaction with this product. E. A. Birse and H. W. Melville [42] have recently determined the efficiency of the re-action of hydrogen atoms with hydrazine in the temperature range 20—200°, the atoms being produced by mercury sensitisation and their concentration measured by the para-hydrogen conversion. The energy of activation is about 7 kg.-cals. and the steric factor is about 10^{-2}; from these results and the conditions of the ammonia photolysis, it is concluded that hydrazine is not responsible for the low stationary atom concentration. In further investigation,[43] it has been shown that photo-decomposing ammonia has no appreciable effect in removing hydrogen atoms at an abnormally fast rate, even when conditions are such that inhibition of ammonia decomposition by hydrogen atoms is to be observed, and the conclusion is drawn that the primary dissociation is not so efficient as has hitherto been supposed.

The determination of the primary reaction efficiency has then been approached in the following way. In a mercury-sensitised conversion of para-hydrogen, the rate of conversion is given by :

$$\mathrm{d}[p_{H_2}]/\mathrm{d}t = k_1[\mathrm{H}][p_{H_2}] + K[\mathrm{H}]/[\mathrm{H}_2] + k_2[\mathrm{H}]^2[\mathrm{H}_2]$$

The first term refers to conversion brought about by the chain atomic exchange reaction, while the other two terms represent rate of conversion due to dissociation of the para-hydrogen molecules, which is equal to the sum of the rates of removal of hydrogen atoms, by diffusion to the walls and by the gas phase triple collision process respectively. In a certain range of fairly low pressures, the second term is predominant; hence

$$\mathrm{d}[p_{H_2}]/\mathrm{d}t = K[\mathrm{H}]/[\mathrm{H}_2]$$

[39] H. W. Melville, *Proc. Roy. Soc.*, 1932, *A.*, **138**, 374.
[40] L. Farkas and P. Harteck, *Z. physikal. Chem.*, 1934, *B*, **25**, 257.
[41] W. Mund and A. van Tiggelen, *Bull. Soc. chim. Belg.*, 1937, **46**, 104.
[42] *Proc. Roy. Soc.*, 1940, *A*, **175**, 164.
[43] *Ibid.*, p. 186.

At the same time the hydrogen-atom concentration is determined by that of the excited mercury atoms; if all the incident light $I_{\text{in.}}$ is absorbed

$$\text{Hg}^* = I_{\text{in.}}/(k_3[\text{H}_2] + k_4)$$

where $k_3[\text{H}_2][\text{Hg}^*]$ is the rate of removal of Hg^* by collision with hydrogen, and k_4^{-1} is the mean life of the excited mercury atom. Since the rate of production of hydrogen atoms $2k_3[\text{H}_2][\text{Hg}^*]$ must be balanced by $K[\text{H}]/[\text{H}_2]$

$$\frac{\text{d}(p_{\text{H}_2})}{\text{d}t} = \frac{2k_3[\text{H}_2]I_{\text{in.}}}{(k_3[\text{H}_2] + k_4)} = \frac{2I_{\text{in.}}}{(1 + k_4/k_3[\text{H}_2])}$$

If k_4 is small compared with $k_3[\text{H}_2]$, the absolute rate of para-hydrogen conversion will be numerically equal to the rate of production of hydrogen atoms. Investigation showed that in a narrow pressure range (approx. 0·4—2 mm. for the given set-up) the rate of conversion was, indeed, independent of the hydrogen pressure. The primary quantum efficiency of ammonia decomposition by zinc-spark radiation was then obtained by the following principle. By adjustment of mercury-vapour lamp and spark intensities, the rate of the mercury-sensitised para-hydrogen conversion at 50 mm. pressure can be made equal to that obtained for 30 mm. of ammonia and 50 mm. of para-hydrogen by the spark. The rate of hydrogen-atom production is then the same for both systems, and is numerically equal to the rate (R) of mercury-sensitised para-hydrogen conversion found for the same intensity of the mercury lamp for a para-hydrogen pressure of 1 mm. The number of spark quanta absorbed ($I_{\text{abs.}}$) by the ammonia can be determined from the rate of the spark decomposition of ammonia and the already known overall quantum yield, *viz.*, 0·3; the efficiency of the primary process is then $R/I_{\text{abs.}}$. The values obtained by E. A. Birse and H. W. Melville [43] range from 0·68 to 0·48, with a mean value of 0·58.

H. J. Welge and A. O. Beckman [44] found that at 1990 A., for small amounts of ammonia decomposition, the product was exclusively hydrogen, and that under certain conditions the overall quantum yields were much higher than 0·3, ranging from 0·74 to 0·95. This is in apparent contrast to the primary value 0·58 (above). The latter value was obtained for 2100 A., and it is known that the yield increases with decreasing wave-length, by an effect on the primary process. It may be noted in this connection that E. O. Wiig [45] found the overall yield of trideuteroammonia decomposition to be greater in the discrete region of absorption at 2138 A. than in the

[44] *J. Amer. Chem. Soc.*, 1936, **58**, 2462.   [45] *Ibid.*, 1937, **59**, 827.

diffuse region at 2100 A. As in the case of formaldehyde, previously discussed, discrete absorption does not necessarily imply induced dissociation; spontaneous processes occurring after different times may be concerned, and the low primary efficiencies may be due to simultaneous degradation of energy. In trideuteroammonia the possibilities of decomposition are (1) $ND_3 \longrightarrow ND_2 + D$, (2) $ND_3 \longrightarrow ND + D_2$; M. Burton [46] points out that, in NH as contrasted with NH_2, all the electrons are paired and that NH may thus resemble CH_2 in behaving more as a reactive molecule than as a free radical. There is then a competition between decomposition into free radicals and one into ultimate molecules in the primary act,[12] in which case the free-radical mechanism will be favoured by decrease in wave-length. If the primary quantum efficiency of the free-radical mechanism is less than that of the decomposition into molecules (reaction 2 requires less energy than reaction 1), the variation of overall yield with wave-length may be explained. The efficiency of secondary reactions will, of course, partly determine the result. Application of the para-hydrogen technique to trideuteroammonia at 2100 A. gave [43] a primary quantum efficiency $(ND_3 \longrightarrow ND_2 + D)$ of 0·28, on the assumption that no error is introduced by taking the exchange conversion initiated by deuterium atoms as kinetically identical with that by hydrogen atoms. The overall yield was 0·21, in agreement with previous measurement.[45]

In the direct photo-decomposition of phosphine,[47] the overall quantum yield was found, by the exchange technique, to be approximately the same (0·50) as that of the secondary processes, and hence the primary quantum efficiency is unity. On the other hand, in the mercury-sensitised decomposition, the over-all yield is 0·27. As would be expected, the yield of the secondary processes is as before 0·50, and the primary efficiency is therefore 0·54; every excited mercury atom which is deactivated does not lead to decomposition of the deactivating phosphine molecule. Similar calculations lead to mercury-sensitised primary efficiency values of : $NH_3 = 0·12$, $ND_3 = 0·02$, $N_2H_4 \not> 0·33$. It is obvious that in a large number of mercury-sensitised reactions the efficiency of the primary decomposition may be much smaller than has been previously supposed. The overall quantum yield for the mercury-sensitised decomposition of methane has been calculated [48] as 0·2 at 196° and 0·008 at 98°. It is therefore probable that at room temperature methane merely quenches the resonance radiation without

[46] J. Chem. Physics, 1938, 6, 680.

[47] H. W. Melville and J. L. Bolland, Proc. Roy. Soc., 1937, A, 160, 384.

[48] K. Morikawa, W. S. Benedict, and H. S. Taylor, J. Chem. Physics, 1937, 5, 212.

decomposition.   The yield of the mercury-sensitised decomposition of ethane at 35° is 0·12, and that of butane 0·55 [49]; in the former, rise of temperature from 100° to 475° approximately doubles the yield,[50] this being attributed to the greater efficiency of the reaction $H + C_2H_6 \longrightarrow C_2H_5 + H_2$.   It is concluded that the mechanism at high temperature is not sensibly different from that at 100°. No mercury-sensitised decomposition of carbon monoxide [51] is found at 2537 A., but at 1849 A. the quantum yield is of the order unity.

Photosensitisations involving metallic vapours other than mercury have previously been limited in number, either for theoretical reasons or by technical difficulties.   Details have, however, been given [52] of a cadmium lamp suitable for photochemical purposes. In mercury–hydrogen mixtures, two hydrogen atoms are produced from one excited mercury atom; although HgH does exist in such systems, inability to secure HgH resonance radiation has been interpreted [53] as evidence that the weak band radiation of HgH is due to molecules formed in excited states and dissociating immediately.   In suitable illuminated cadmium–hydrogen mixtures, CdH resonance radiation is observed; an excited cadmium atom in collision with a hydrogen molecule produces CdH in the normal state.   The initial action in the case of ethane (3261 A.) is then

$$Cd(^3P_1) + C_2H_6 \longrightarrow C_2H_5 + CdH$$
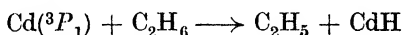
and the overall quantum yield [54] in the initial stages of the reaction is of the order 0·4 at 278°.   Similar values were obtained for propane and butane.   The cadmium-sensitised reactions of ethylene in absence and in presence of hydrogen have also been studied.[55]

A general table of other quantum yields has been given by F. Daniels.[56]   It may be emphasised that recent work on the chloroacetic acid hydrolysis, often used as a standard in photochemical work, has shown that the quantum efficiency is less than the unit value previously accepted.   R. N. Smith, P. A. Leighton, and W. G. Leighton [57] report a value for 2537 A. of 0·31 at 25°, increasing as the temperature rises to 0·69 at 69°, and L. B. Thomas [58] finds in

[49] E. W. R. Steacie and N. W. F. Phillips, *J. Chem. Physics*, 1938, **6**, 179.

[50] E. W. R. Steacie and R. L. Cunningham, *ibid.*, 1940, **8**, 800.

[51] J. E. Cline and G. S. Forbes, *J. Amer. Chem. Soc.*, 1939, **61**, 716.

[52] E. W. R. Steacie and R. Potvin, *J. Chem. Physics*, 1939, **7**, 782; *Canadian J. Res.*, 1938, *B*, **16**, 337.

[53] L. O. Ollsen, *J. Chem. Physics*, 1938, **6**, 307.

[54] E. W. R. Steacie and R. Potvin, *ibid.*, 1939, **7**, 782.

[55] *Idem, Canadian J. Res.*, 1940, **18**, *B*, 47.

[56] *J. Physical Chem.*, 1938, **42**, 711.

[57] *J. Amer. Chem. Soc.*, 1939, **61**, 2299.

[58] *Ibid.*, 1940, **62**, 1879; see L. Küchler and H. Pick, *Z. physikal. Chem.*, 1939, *B*, **45**, 116.

confirmation 0·34 at 25°. Although this reaction may, as before, be used as a standard of actinometry from the point of view of independence of quantum efficiency on moderate variations of concentration and light intensity,[59] care must obviously be taken in its application to the determination of other efficiencies. The uranyl oxalate decomposition is reported similarly [60] to have an efficiency value of 0·60.

Reaction Kinetics.—At one time it was customary to divide photochemical reactions into two groups, the direct dissociation type and the activated molecule type, where, in the latter, decomposition followed the collision of the activated molecule with a second unactivated molecule of similar kind. The number of reactions to which such a mechanism can be now applied is very small. The quantum efficiency of the trideuteroammonia decomposition, examined by E. O. Wiig on this basis,[45] may be explained in other ways, as previously discussed.[46] Also, the quantum efficiency of the nitrosyl chloride decomposition at wave-lengths greater than 5300 A. is independent of its pressure down to 7 mm. pressure and is unaffected by added nitrogen or carbon dioxide [61]; accordingly, the dissociation mechanism is favoured for this region as well as for the continuum for wave-lengths less than 5300 A.

In the halogens, the results of absorption of a quantum of radiation are generally well known for gaseous systems, and interest in reactions involving halogen absorption has usually centred in the kinetics of the secondary chemical processes following dissociation. The form of the expression for the overall quantum efficiency is frequently determined by the recombination processes of the halogen atoms. It has been largely photochemical evidence which has established the fact that the recombination of two bromine or two iodine atoms requires in effect a triple collision involving a third partner, but it is doubtful if in illuminated chlorine the analogous process will serve to explain the experimental results. In the last Report [1] mention was made of the possible removal of chlorine atoms by collision with chlorine molecules to give Cl_3 complexes, these decomposing reversibly as well as by mutual recombination. The necessity for the introduction of such complexes has not been universally admitted; M. Bodenstein, W. Brenschede, and H. J. Schumacher remark [62] that there are no grounds for such assumption on the basis of the other numerous

[59] See, however, ref. (50), p. 802.
[60] W. G. Leighton, R. N. Smith, and P. A. Leighton, *J. Amer. Chem. Soc.*, 1938, **60**, 2566.
[61] G. L. Natanson, *Acta Physicochim. U.R.S.S.*, 1939, **11**, 521.
[62] *Z. physikal. Chem.*, 1938, *B*, **40**, 125.

investigations involving illuminated chlorine, and that the work of A. J. Allmand and his co-workers [63] is to be explained on other lines. The postulation of the Cl_3 complex here depends largely on the lower quantum yield observed in the hydrogen–chlorine combination at higher chlorine concentrations, this being attributed to a retardation of the rate by chlorine by the reaction $Cl + Cl_2 \longrightarrow Cl_3$. W. A. Alexander and H. J. Schumacher [64] point out that if the light absorption is great and the reaction velocity large, convection may be an important factor,[65] in which case wall action may be responsible for the reduced rate by surface removal of chain carriers. On the other hand, study of the Budde effect in chlorine in the presence of other added gases [66] shows that, although convection does occur as judged by measurement of relative thermal conductivities of the gas mixtures in the same vessel under the same pressure and temperature conditions, yet such convection effects were approximately the same for all the added gases, and hence the differences observed in the Budde effect, after allowance for diffusion and thermal conductivity, are such as to support the formation of Cl_3 by triple collisions of different efficiencies $(Cl + Cl_2 + M \longrightarrow Cl_3 + M)$.

It is intended shortly to publish further work [67] on the hydrogen-chlorine reaction from this point of view; results are interpreted as supporting the Cl_3 hypothesis, and show that under certain conditions retardation to different degrees results in the gas phase from the presence of other added M molecules, as well as by hydrogen chloride acting in this capacity. The apparent discrepancies between the results and formulæ obtained by different workers in this and other reactions may be due to the non-recognition of the possible effects of such third-partner molecules. It has been generally assumed that the collision efficiency of such triple collisions is unity; experiment has in some cases shown this to be true,[68] but in certain other instances, some small degree of activation may be necessary.

The photochemical formation of carbonyl chloride from carbon monoxide and chlorine has been exhaustively reviewed in relation to the thermal reaction by M. Bodenstein, W. Brenschede, and H. J. Schumacher [69] on the basis of the reversible equilibrium

[63] G. V. V. Squire and A. J. Allmand, *J.*, 1937, 1869; H. C. Craggs, G. V. V. Squire, and A. J. Allmand, *ibid.*, p. 1878.

[64] *Z. physikal. Chem.*, 1939, *B*, **44**, 322.

[65] See W. Franke and H. J. Schumacher, *ibid.*, 1939, *B*, **42**, 320, 321.

[66] M. Ritchie and R. L. Smith, *J.*, 1940, 394.   [67] M. Ritchie and D. Taylor.

[68] Recombination of bromine atoms; K. L. Müller and H. J. Schumacher, *Z. physikal. Chem.*, 1939, *B*, **42**, 327.

[69] *Ibid.*, 1938, *B*, **40**, 121.

formation of COCl [70] from CO, Cl, and a third molecule. The chlorine-sensitised oxidation of carbon monoxide has been further investigated at low total pressures (10—100 mm.) [71]; as at higher pressures, the rate is proportional to the square root of the monoxide pressure. Discussion of observed ratios of carbon dioxide to carbonyl chloride formation in such systems leads to the postulation of the intermediate CO_3Cl formed from oxygen and COCl,[72] the mode of decomposition of such a complex depending on the temperature.

The reaction between chlorine and CCl_3Br [73] involves Cl and CCl_3 as chain carriers; the chlorine-sensitised oxidation of CCl_3Br is much faster than the corresponding bromine reaction, both being of complex character [74] and yielding carbonyl chloride, chlorine, and bromine. The reaction between chlorine and chloral [75] produces carbon tetrachloride, carbon monoxide, and hydrogen chloride, also by a chain mechanism involving CCl_3CO as a chain carrier, stable under the given conditions (70—90°); chains are broken by its bimolecular decomposition. The corresponding oxidation [76] yields carbonyl chloride, carbon monoxide, and hydrogen chloride, the rate being determined by the amount of absorbed light only; peroxide formation of the type CCl_3,CO,O_2 is here assumed.

The photobromination of dichloroethylene,[77] although complicated by the reverse reaction, resembles in many respects the photosynthesis of hydrogen bromide. At low pressures, bromine atoms are removed at the vessel surfaces, the rate thus rising as diffusion to the wall is prevented by the addition of carbon dioxide or helium; at high pressures a retardation is found owing to the recombination of bromine atoms by triple collisions, with a corresponding change in the $I_{abs.}$ factor of the rate expression. The radical involved in the chain mechanism is $C_2H_2Cl_2Br$; a quantum yield of 10^3 is recorded for certain conditions, that of the reverse reaction being of the order 10. In the bromination of acetylene,[78] which is somewhat similar in kinetics, a quantum yield of over 10^4 has been recorded; increased pressure raises the rate to a maximum by prevention of diffusion of bromine atoms to the wall, but at high pressures, by reason of the high rate of reaction, convection effects are such as to

[70] See also W. Brenschede, Z. physikal. Chem., 1938, B, 41, 237.

[71] W. Franke and J. H. Schumacher, ibid., 1938, B, 40, 115.

[72] W. Brenschede, ibid., 1938, B, 41, 254.

[73] H. J. Schumacher, ibid., 1939, B, 42, 324; cf. H. G. Vesper and G. K. Rollefson, J. Amer. Chem. Soc., 1934, 56, 1455.

[74] W. Franke and H. J. Schumacher, Z. physikal. Chem., 1939, B, 42, 297.

[75] W. A. Alexander and H. J. Schumacher, ibid., 1939, B, 44, 57.

[76] Idem, ibid., p. 313.

[77] K. L. Müller and H. J. Schumacher, ibid., 1939, B, 42, 327.

[78] Idem, ibid., 1938, B, 39, 352.

keep the rate approximately proportional to $I_{abs.}$, with surface removal of bromine atoms still predominant. There is no necessity for consideration of a Br_3 complex.[79] The photochemical formation of trichlorobromomethane from chloroform and bromine is again somewhat similar to that of hydrogen bromide and to the reaction between chlorine and chloroform.[80]

The gas-phase kinetics of the photolysis and iodine-sensitised decomposition of $C_2H_4I_2$ [81] probably resemble those of the corresponding reactions in carbon tetrachloride solution [82]; both involve the radical C_2H_4I. Thermal reaction is considerable in both cases.

Analysis of kinetics of photohalogenation in solution is in general complicated by the fact that an appreciable concentration of halogen atoms will not be reached even when the radiation is such as to produce complete dissociation in the gas phase, by reason of the cage-effect of solvent molecules and the resulting primary recombination. The nature of the reacting species may then be uncertain. Quantum yields will tend to be low. A value of approximately 0·01 is recorded [83] for the action of illuminated bromine on bromo-benzene in carbon tetrachloride; although there is no appreciable thermal reaction at ordinary temperatures, the postulated mechanism involves two secondary thermal reactions following the primary addition reaction between activated bromine molecules and the bromobenzene. No substitution reactions were here observed. The photochemistry of di-iodoacetylene and tetraiodoethane in hexane has been studied [84]; in aqueous solution, the photoreaction between bromine and hydrogen peroxide [85] and the photo-oxidation of the nitrite ion by bromine [86] have also been investigated.

A comprehensive review of photochemistry in the Schumann ultra-violet has been given by W. Groth.[87]

The analysis of the kinetics of such systems is, of course, greatly facilitated by the ease with which the light intensity may be altered, the concentration of chain carriers or other intermediates being thus varied by a method which largely avoids the introduction of other complicating factors. Some recent extensions of such technique may be briefly considered. H. W. Melville and his co-

[79] Cf. J. E. Booher and G. K. Rollefson, *J. Amer. Chem. Soc.*, 1934, **56**, 2288.

[80] V. Braunwarth and H. J. Schumacher, *Kolloid-Z.*, 1939, **89**, 184.

[81] W. H. Janneck and E. O. Wiig, *J. Amer. Chem. Soc.*, 1940, **62**, 1877.

[82] Cf. H. J. Schumacher and E. O. Wiig, *Z. physikal Chem.*, 1930, *B*, **11**, 45.

[83] D. L. Hammick, J. M. Hutson, and G. I. Jenkins, *J.*, 1938, 1959.

[84] J. W. Tamblyn and G. S. Forbes, *J. Amer. Chem. Soc.*, 1940, **62**, 99.

[85] A. E. Callow, R. O. Griffith, and A. McKeown, *Trans. Faraday Soc.*, 1939, **35**, 412.

[86] *Idem, ibid.*, p. 559.   [87] *Z. Elektrochem.*, 1939, **45**, 262.

workers have made considerable use of the "arc plus spark" technique, where the combined effects of light of two wave-lengths are considered in relation to the effects of each observed separately. For instance, in the photolysis of ammonia,[43] where the removal of hydrogen atoms by some reacting species is a possibility, examination has been carried out on the principle of decomposing ammonia in the presence of hydrogen atoms, and by observing, by the para-hydrogen method, whether the hydrogen-atom concentration is reduced thereby. Hydrogen atoms were thus produced from hydrogen by mercury vapour and the mercury arc giving the resonance line 2537 A., while in the same vessel ammonia was directly decomposed by 2100 A. radiation from a zinc spark. In this particular case the ratio of the combined rate of para-hydrogen conversion (spark plus arc) to the sum of the rates produced by spark and arc separately was unity, indicating that photodecomposing ammonia had no appreciable effect on removing hydrogen atoms at an abnormally fast rate.

Similar technique has been employed in attempts to determine the mean life-time of the NH_2 radical for given conditions. The use of the rotating sector for such general purposes (e.g., the life-time of the fluorescing diacetyl molecule [88]) is well known. In the ammonia decomposition, the basis of the method was to generate hydrogen atoms and NH_2 radicals at known time intervals. At sufficiently small intervals, NH_2 radicals, if generated first, will be removed by subsequently formed hydrogen atoms, by the reaction $H + NH_2 \longrightarrow NH_3$; at larger intervals the NH_2 radicals may be otherwise removed and no inhibition of the ammonia decomposition will be found. At some intermediate interval inhibition might just be observed, this then giving an indication of the life-time of the radical. The light beams from the mercury lamp and the spark were at right angles to each other and entered the reaction vessel through a slit in a concentric revolving cylinder. With this arrangement the ratio of rate of spark alone to the difference between combined rate and arc alone $[S/(SA-A)]$ was observed to be greater than unity, thus indicating inhibition, not only at small time intervals but also at the large interval of 70 secs.

An interesting extension of such methods of determining the life-time of short-lived molecules has been described for the case of the methyl acrylate photopolymerisation.[89] If two sharply defined beams of light of equal intensity and separated by a considerable distance are allowed to fall on the vapour, the total rate of polymerisation will be the sum of the rates produced by each separately.

[88] G. M. Almy and S. Anderson, J. Chem. Physics, 1940, 8, 805.

[89] T. T. Jones and H. W. Melville, Proc. Roy. Soc., 1940, A, 175, 392.

If, however, the active species carrying on the chain process is removed by mutual recombination (rate of removal of $P \propto P^2$), superposition of the beams will give a total rate $\sqrt{2}$ times that of each separately. As the distance between the beams is increased, there will be a gradual increase in rate to $\sqrt{2}$ times the superimposed value, and hence the distance at which the rate has the mean value $\frac{1}{2}(1 + \sqrt{2})$ will be a measure of the distance of diffusion of the active species, this in turn being connected with the mean life-time. The theory of the relationship between diffusion and mean life-time has been worked out in detail for the case of hydrogen atoms, where the various factors of diffusion, recombination, and mean life-time are known, and comparison then made between calculated and known values. Extension of such calculation to the polymerisation of methyl acrylate indicates a mean life-time of the active polymer as 1·8 secs. for given conditions; the absolute value of the reaction velocity coefficient between active polymer and monomer and the steric factor may consequently be estimated.

Reactions in Solids.—In the last few years considerable advance has been made in the theoretical and experimental study of absorption in solids,[90] but there are few direct measurements of the quantum efficiency of photochemical reactions under such conditions, mainly because of the difficulties of measuring the light energy absorbed and of ensuring uniform exposure of the solid. C. F. Goodeve and J. A. Kitchener [91] describe a method in connection with the decomposition of the dye Chlorazol Sky Blue adsorbed on titanium dioxide, whereby the quantum efficiency has been found for light of 3650 A. and the change of efficiency studied for the approximate range 7200—3200 A. The quantum efficiency in the extreme red is negligible but rises to a steady value of approximately 2×10^{-5} for the region in which the dye absorbs strongly. A sharp rise is found at the shorter wave-lengths corresponding to the threshold of absorption by the dioxide. Measurement at 3650 A. indicated in the earlier stages of illumination some inhibitory action, succeeded by a rise in quantum efficiency dependent on the concentration of " vulnerable " dye molecules; in the later stages, the efficiency decreased more rapidly than the total concentration of unbleached dye, this being taken to indicate that some dye molecules, by reason of their arrangement on the surface, do not undergo photosensitisation by the dioxide.[92] The photochemical oxidation of ammonia to nitrous acid in aqueous solution is also sensitised by titanium dioxide.[93]

[90] Cf. *Ann. Reports*, 1938, **35**, 85.   [91] *Trans. Faraday Soc.*, 1938, **34**, 570.

[92] Cf. C. F. Goodeve and J. A. Kitchener, *ibid.*, p. 902.

[93] G. G. Rao, *Z. physikal. Chem.*, 1939, **184**, 377.

Barium and strontium azides are decomposed by ultra-violet light at room temperature, the thermal decomposition being accelerated by suitable pre-illumination.[94] The threshold for the absorption of ultra-violet light by azide ions in solution and in the solid state is 2600—2700 A., and that for the photochemical reaction is in the same region; prolonged illumination with light of wavelength less than 2360 A. produced nuclei of metallic barium. Parahydrogen is formed by mercury-arc illumination of solid hydrogen iodide at low temperature, but normal hydrogen is formed by the photolysis of formaldehyde and methyl alcohol under the same conditions.[95] This is taken to indicate that the two hydrogen atoms forming a molecule come from the same formaldehyde or methyl alcohol molecule.

New Publications.—Mention may be made of "Photochemistry and the Mechanism of Chemical Reactions" (Prentice-Hall Inc., New York) by G. K. Rollefson, reviewed by P. A. Leighton.[96] General photochemical technique is described in "Experimental Methods in Gas Reactions" (Macmillan & Co., Ltd.) by A. Farkas and H. W. Melville.   M. R.

5. COLLOIDS.

Within the last ten years the whole face of colloid chemistry has changed. Previously, direct application of the methods of chemistry and physical chemistry were rare, such as the work of Loeb, and were little more than groping in the dark. To-day the molecular weights of molecules examined and synthesised have increased to at least a million—a thousandfold increase. This is due primarily to the recognition that polymer molecules are built up from small simple repeating units and that naturally occurring substances such as the proteins are also definite giant molecules whose molecular weight can be determined. It is true that this advance has been largely due to the introduction of new methods of attack such as the ultracentrifuge and X-rays, but the classical colloid property of high viscosity has also played an important part. At the same time, advances in surface-film research have opened up an entirely new field, but it is a field which does not properly belong to colloids, although the association is close. The surface properties of longchain amphipathic molecules are properties of molecularly dispersed substances, whereas the true colloidal ones are due to the micelles.

[94] W. E. Garner and J. Maggs, *Proc. Roy. Soc.*, 1939, *A*, 172, 299.
[95] A. Farkas and L. Farkas, *J. Amer. Chem. Soc.*, 1939, 61, 3393.
[96] *Ibid.*, p. 2567.

It is somewhat ironical that the micellar colloids, such as the soaps, which were formerly expected to throw light on more complex lyophilic colloids, are now relegated to a comparatively small sub-group. At the same time serious attempts are being made to provide an exact theoretical treatment of hydrophobic sols on the basis of a diffuse double layer and surrounding ionic atmosphere, the Debye–Hückel equation being used. It is easy to see how far we have advanced from the old facile phrase that " Colloid chemistry is the chemistry of surfaces," in which was meant the reduction of interfacial energy by adsorption.

To see the present position, it is necessary to consider the sizes of colloid particles of the various types. Formerly, the size was so large that there was no continuity from normally sized molecules to colloid particles. Now, the range is continuous. Formerly, Brownian motion was often used as a size-limiting criterion. Now, we have continuity from small Brownian motion in the largest particles to ordinary heat motion in the smaller ones, so that we cannot make the arbitrary division between crystalloid and colloid on this ground any more. Emulsions contain particles with diameter from 0.5 to 5μ; hydrophobic sols range from a few $\mu\mu$ to more than $100\mu\mu$. About 5μ is the upper limit for observable Brownian motion. Micellar colloids, such as the soaps, have " molecular weights " of the order of 15,000. On the other hand, polymers range from less than 100 to more than a million. Hydrophobic sols are well above the million mark. The polymer molecules illustrate particularly that mere size alone is not enough; their shape, or length/breadth ratio, is of the greatest importance. Here we get continuity between the long polymers and the classical cases of non-spherical, hydrophobic sols such as vanadium pentoxide.

Our present position is that we enquire how molecules aggregate to form colloid particles; i.e., what shape is the particle and why is it stable ? The first part still requires the idea of reduction of free surface energy in hydrophobic and micellar colloids. In polymers, reaction kinetics provide the answer. Stability of the aggregation colloids depends upon their charge and the surrounding ionic atmosphere, whereas in polymers solubility is true solubility, though we must regard the layer of solvent around the particles as more closely bound than in ordinary crystalloidal solutions. We thus return to a conception of solvation which, however, is quite different from and less vague than the older theories of solvation.

Hydrophobic Sols.

The problem of the stability of hydrophobic sols, of their electrical properties, and of their coagulation has received much attention

lately. H. R. Kruyt [1] has summarised the position excellently as follows :

1. Why do particles of a mere suspension tend to adhere to each other ? (question of attraction).

2. What must be done to prevent this ? (question of peptisation).

3. What promotes coalescence ? (question of flocculation).

He then points out that Question 1 was in the past answered by the concept of reduction of free surface energy, but that the van der Waals forces responsible fall off as a high power of the distance from the surface. This shortness of range is difficult to reconcile with much experimental evidence. As regards Question 2, the older concept of the electric double layer paid insufficient attention to the origin of the double layer and to its nature. The problem of coagulation is complicated by the opposite explanations : by the adsorption theory, whereby all changes of stability are explained as changes of the number of charging ions and adsorption of discharging ions; or by Gouy's restoration of the Helmholtz concept of the diffuse double layer which explains the changes by disturbance of the "gegenion" atmosphere. E. K. Rideal,[2] puts the matter in another way. The colloid particle may be regarded as a very large ion, whose charge arises from surface ionisation. Hence, all such particles must be ionogenic. On the other hand, we may assume that there is adsorbed at the interface an electrolyte as ion-pairs of which one ion is held more firmly than the other which wanders away into the solution. It is obvious that, in a sol free from coagulating electrolyte, stability is determined solely by the behaviour of the particles towards each other.

The logical origin of the present attempts to visualise the state of affairs and to provide a theoretical treatment is to be found in the recognition of the difference between ε and ζ potentials. The ε potential is the potential from the interface to the bulk of the dispersion medium, whereas the electrokinetic potential is that between bulk of solvent and exterior of the layer of liquid adhering to the interface. The ζ potential is therefore that across part of a diffuse double layer (Gouy, von Smoluchowski, Stern).

H. C. Hamaker [3] has drawn curves in two dimensions of the profile of the potential/distance-from-particle relation, and has outlined the types. S. Levine and G. P. Dube,[4] I. Langmuir,[5] B. Derjaguin,[6]

[1] Ned. Chem. Ver., Symposium on Hydrophobic Colloids, 1937, 7.

[2] *Trans. Faraday Soc.*, 1940, **36**, 1.   [3] Ned. Chem. Ver., 1938, 16.

[4] *Trans. Faraday Soc.*, 1939, **35**, 1125; 1940, **36**, 215; S. Levine, *Proc. Roy. Soc.*, 1939, **170**, *A*, 145, 165; *J. Chem. Physics*, 1939, **170**, 165.

[5] *Ibid.*, 1938, **6**, 873.   [6] *Trans. Faraday Soc.*, 1940, **36**, 203.

and others have followed this method to calculate the conditions of stability and coagulation of hydrophobic sols. The potential curve is the sum of the van der Waals and the electrical forces. The general result is that, at some distance from the particle surface, there is a minimum. The energy function exhibits a maximum close to the particle and a minimum further out. Inside the maximum the particles are attracted; outside, repulsed. There is naturally a tendency to correlate this minimum with the appearance of thixotropy, and some workers have assumed that orientation of aniso-dimensional particles is a requisite for gelation due to these forces. However, we see later (p. 119) that this picture is impossible on experimental grounds, but the nature of the forces of attraction is not considered in the problems of irregular packing of the particles which is shown to be the first requisite. The connection between the minimum and the properties of pastes is obvious. The original papers of Levine and Dube and of Derjaguin and the discussion [7] should be consulted. E. J. W. Verwey [8] also suggests that, in cases of emulsions, in which the charge cannot be raised to a value large enough for stability, an emulsifier shifts the double layer potential drop towards the outer phase. Solid emulsifiers are also thought to act in the same manner.

Micellar Colloids.

The best known micellar colloids are those formed by the soaps and similar " paraffin-chain " salts. This name has been introduced to cover a large number of synthetic substances used during recent years as detergents and wetting agents. G. S. Hartley's epithet " amphipathic " admirably describes these substances which, as J. W. McBain first recognised, are molecules consisting of polar and non-polar parts in a molecule large enough for each to exert its own properties. For instance, the paraffin-chain is insoluble in water while the end groups $-CO_2Na$, $-HSO_3$, $-NH_2$, etc., are soluble. Aggregation of the paraffin chains reduces the interfacial energy at the paraffin–water interface, and micelles are built up with a water-soluble exterior. Their size seems to be well defined, probably because it is determined by the packing of the exterior polar groups. Some of these are ionised. A valuable account of these substances and their synthesis has been published by H. K. Dean.[9]

The constitution of solutions of paraffin-chain salts mentioned in

[7] *Trans. Faraday Soc.*, 1940, 36, 711.   [8] Ned. Chem. Ver., 1937, 58.

[9] Report of Symposium on Wetting and Detergency (Leather Trades Chemists Society) (A. Harvey, 1937). See also F. E. Bartell, *Ind. Eng. Chem.*, 1939, 36, 31; and, as emulsifiers, W. Clayton, " Technical Aspects of Emulsions," p. 9 (Leather Trades Chemists Society) (A. Harvey, 1935).

the *Annual Reports* for 1936 [10] is now generally accepted, and a considerable amount of further evidence has been found for the abrupt change of properties at the critical concentration at which micellar aggregation sets in. C. R. Bury's demonstration that the law of mass action requires a very rapid increase in colloidal association at this point has been confirmed by G. S. Hartley and others.[11] If C is the concentration of soap, x the fraction aggregated, and K the equilibrium constant, then

$$K = n[C(1 - x)]^n/Cx.$$

The form of this equation explains the steep rise of solubility of soaps which occurs over a few degrees.*

N. K. Adam and H. L. Shute [12] measured the surface tension of dilute soap solutions and its variation over long periods by means of the sessile drop method. In very dilute solutions, σ falls slowly for a week or more, finally very nearly reaching the value for concentrated solutions. For a chain of sixteen carbon atoms the critical concentration, c, was M/1000, and for the twelve-carbon chain, M/100. Salts reduce c but without altering the final value of σ. J. Powney and C. C. Addison [13] also measured surface tension against air and interfacial tensions against xylene for some soaps. Table I gives their values for c; 0·1% of sodium hydroxide was added to suppress hydrolysis, since this affects the value of c.

<div align="center">

TABLE I.

</div>

Soap.	c (molar). From σ against air.	From σ against xylene.
Sodium laurate	0·021	0·020
,, myristate	0·0029	0·0029
,, palmitate	0·00065	0·00065
,, stearate	0·000075	—

J. Powney and L. J. Wood [14] found the electrophoretic mobility to reach a maximum at the critical concentration—M/100 for sodium laurate. Variations were found with chain length and also marked temperature changes. E. E. Wark and I. W. Wark,[15] working with trimethylcetylammonium bromide, sodium cetyl sulphate, and potassium laurate, found that flotation ceases to be effective at c. R. C. Palmer and E. K. Rideal [16] measured adhesion numbers at 45° and found minima at :

<div align="center">

Dodecyl sodium sulphate............ M/100
Cetyl sodium sulphate 3M/1000
Cetylpyridinium bromide............ 3M/1000

</div>

[10] P. 110.   [11] "Paraffin-chain Salts." (Hermann, 1936.)
[12] *Trans. Faraday Soc.*, 1938, **34**, 758.   [13] *Ibid.*, p. 372.
[14] *Ibid.*, 1939, **35**, 420.   [15] *Nature*, 1939, **143**, 856.   [16] *J.*, 1939, 573.
* First observed by Krafft, and since named the "Krafft point."

J. Stauff [17] determined the hydroxyl-ion activities of sodium soaps potentiometrically and found the activity to increase with increasing concentration up to the critical value : log c falls linearly with increase of chain length.　K. Hess, W. Philippoff, and H. Kiessig [18] concluded from X-ray examination of solutions that the soap is present as molecules, amorphous micelles, and crystalline micelles. G. S. Hartley and D. F. Runnicles [19] deduced from diffusion experiments that the micelle of cetylpyridinium salts has a diameter of 52 A.

The more concentrated solutions of the soaps and the pure soaps themselves continue to provide problems.　The soaps are perhaps uniquely complicated among the paraffin-chain salts ; nevertheless, their behaviour is of theoretical and practical importance.　J. W. McBain's phase-rule studies of soap–water systems have been continued for sodium palmitate–sodium chloride–water at 90°,[20] sodium laurate–sodium chloride–water,[21] and sodium palmitate–sodium laurate–sodium chloride–water at 90°.[22]

A. S. C. Lawrence [23] has prepared a number of soaps in pure condition.　On heating, sharp melting points are not obtained, but when the isotropic liquid is cooled most of the substances pass through a plastic state which on further cooling changes into microcrystalline solid.　Cases examined by X-rays gave only a side spacing in the plastic region, but showed the low-temperature modification to be fully crystalline.　Of the stearates, those of lead, zinc, and thorium did not exhibit the plastic phase, and zinc oleate also failed to show this modification.　It is shown that many of the melting points recorded for the metal soaps are incorrect.[24]　R. D. Vold and M. J. Vold [25] have shown that sodium palmitate exists in six phases between 70° and 320°.　Their existence was established by a dilatometric method, supplemented by microscopic investigation in polarised light.　Four of these phases are believed to be liquid-crystalline, but their nature so far is obscure.　The phases distinguished with certainty are shown in the table, together with transition temperatures and mean coefficients of expansion.

Phase change.	Temp.	Vol. increase, c.c./g.
Curb fibres to sub-waxy soap	117°	0·0085
Sub-waxy soap to waxy soap	135	0·0148
Waxy soap to sub-neat soap	208	0·027
Sub-neat soap to neat soap	253	0·0035
Neat soap to isotropic liquid	292	0·0021

[17] *Z. physikal. Chem.*, 1938, **183**, 55.　　[18] *Kolloid-Z.*, 1939, **88**, 40.
[19] *Proc. Roy. Soc.*, 1938, *A*, **168**, 420.
[20] *J. Amer. Chem. Soc.*, 1938, **60**, 2066.　[21] *Ibid.*, p. 1870.
[22] *Ibid.*, 1939, **61**, 30.　　　　[23] *Trans. Faraday Soc.*, 1938, **34**, 660.
[24] J. Braun, "Die Metallseifen," Leipzig 1932.
[25] *J. Amer. Chem. Soc.*, 1939, **61**, 808.

These results may be compared with those of sodium laurate–water systems,[26] and also with the mesophase postulated in mono-layers,[27] although it is impossible to see how a monolayer can be liquid-crystalline in either the classical smectic or the nematic state. R. D. Vold [28] has described the liquid-crystalline phases in sodium oleate–water systems, and has attempted to correlate these with other liquid-crystalline systems. Illustrations are given, but further examination, perhaps by X-rays, is needed before their constitution can be determined. The following table summarises the results for sodium laurate–water.

Phase.	Composition range.	
	Soap, wt. %.	Soap, mols. %.
Isotropic solution	0—35·8	0·00—4·4
Middle soap	38—52	4·80—7·95
Neat soap	55·4—75	9·1—19·5
Waxy soap	77—88	21·2—36·3
Curd fibre	91·3—100	45·2—100

The intermediate phases in the anhydrous soap may be compared with J. D. Bernal's results [29] for thallous stearate, which shows a smectic phase well defined by its layer flow. K. Hermann [30] made an X-ray examination of the smectic and the solid phases, but Bernal's closer optical examination of the transition disclosed much greater complexity. At a few degrees below the melting point, the substance becomes uniaxial; on further cooling, the axes cross and it becomes increasingly biaxial. At about 100° there is an abrupt change and another form with smaller birefringences but with the same orientation appears. This is the form stable at room temperature. Unpublished photomicrographs taken in polarised light by the Reporter disclose four textures between liquid and solid. The Reporter also observed that the colour of the first phase appearing below the melting point was invariably yellow (with crossed Nicols), and that the intermediate phases of sodium stearate are also yellow— an observation recorded by Vold and Vold in the case of the waxy phase of sodium palmitate. This curious uniformity in samples whose thickness varied from a small fraction of a mm. up to 0·5 mm. may be due to orientation at the glass surfaces—a phenomenon already observed to occur most persistently in other nematic liquid-crystalline substances.[31]

[26] *J. Amer. Chem. Soc.*, 1939, **61**, 37.

[27] D. G. Dervichian, *J. Chem. Physics*, 1939, **7**, 931.

[28] *J. Physical Chem.*, 1939, **43**, 1213.

[29] *Trans. Faraday Soc.*, 1933, **29**, 1074.

[30] *Ibid.*, p. 973.

[31] M. G. Friedel, *Ann. Physique*, 1922, **18**, 271, 474.

Internal Solubility in Soap Micelles and Peptisation.

Water-insoluble Substances.—S. U. Pickering [32] stirred oil into concentrated soap solutions and obtained systems which he described as emulsions.   The oil content was 99% in one case.   His method of analysis contains an error which reduces this value to 95·2%, but, in actual fact, his " clear lumps of gel " were not emulsions at all. Under the microscope they can be seen to be pastes of very thin plates of solid soap dispersed in the oil.   Pickering also found, however, that, on diluting his oil–soap–water pastes, he obtained two layers—one of emulsion and one of clear soap solution which still contained oil.   A direct analysis of these sols has been made by A. S. C. Lawrence,[33] who found that in one case 100 c.c. of clear sol contained 2·74 g. of potassium oleate and 2 c.c. of " Nujol." This, however, was not the maximum amount of oil which could be dissolved.   Lawrence used a simpler and more direct method of determining solubilities of oil in which 90% alcohol was used as solvent.*   In the absence of soap the " Nujol " is insoluble, so the amount dissolved by the soap can be determined directly.   The saturation values for 100 g. of soap dissolved in 2000 c.c. of 90% alcohol were :

Soap.	" Nujol " dissolved, c.c.
Sodium stearate	110
Potassium stearate	170
Cæsium stearate	200
Sodium laurate	80

G. S. Hartley [34] measured the solubility of *trans*-azobenzene in aqueous solutions of cetylpyridinium salts by a colorimetric method, and found that it was proportional to the concentration of paraffin-salt ions over a wide range of concentration of the soap.   The solubility fell off abruptly below the critical concentration at which micelle formation starts.   J. W. McBain and T. M. Woo [35] measured the solubility of a water-insoluble † dye in laurylsulphonic acid solutions.   The dye was dissolved either from the solid state or from toluene solution.   Maximum solubility (per unit weight of soap) was found in the most dilute solution.   Solubilities in other soap solutions are also given as empirical " dye numbers," which were derived from the distribution of dye between soap and toluene solutions.   In contrast to the above result, solubility was zero in the homologous potassium soaps of the saturated carboxylic series up to the octoate. That is, solubility appears only when micelles are present.   McBain

[32] *J.*, 1907, **91**, 2001; 1917, **111**, 95.
[33] *Trans. Faraday Soc.*, 1937, **33**, 815.
[34] *J.*, 1938, 1968.   [35] *J. Physical Chem.*, 1938, **42**, 1099.
* The soap is still colloidally dissolved in this mixture.

and Woo criticise the experiments of other workers on the ground that formation of unstable von Weimarn sols is not guarded against. The experiments of Hartley and Lawrence show that equilibrium was reached without supersaturation, so the criticism is invalid.

Water-soluble Substances.—As early as 1886 [36] it was shown that soap lowers the consolute temperature of phenol–water and cresol–water systems. A. S. C. Lawrence [37] pointed out that glycerol improves soap solutions for blowing bubbles by peptising them, and that the improvement cannot be due to an increase of viscosity, as previously assumed, since this is reduced. E. Angelescu and D. M. Popescu [38] examined the effects of a number of soaps upon the *o*-cresol–water system and found that the solubility of the cresol was increased. They found the viscosity of the ternary system to pass through a maximum, after which it fell to a small value on further addition of cresol. The maximum was attributed to an intermediate degree of dispersion of the soap. They suggested that the final dispersion of the soap was molecular. E. Lester Smith [39] also observed increased solubility in water of cresols and ethyl acetate in the presence of soap, and concluded that the phenomenon could not be due to adsorption and that the increase of solubility was mutual. Lawrence [40] found that sodium soap solutions were peptised by alcohols, amines, and phenols. Peptisation occurs first in the homologous series at the C_8 soap. Sodium stearate solutions are saturated by amyl alcohol at 6 mols. of alcohol per mol. of soap; for hexyl and heptyl alcohols the figure was about 4, and for oleyl and cetyl about 1. For aniline, the value was 7, but from setting-point curves it was concluded that peptisation ended at 4 mols. and that the extra three were dissolved internally. This suggestion was supported by the ease with which the first four were taken up as compared with the sluggish solution of the last three. Fig. 1 [41] shows diagrammatically the possible cases : (*a*) is that of peptisation by a water-soluble substance, (*b*) that for a water-insoluble one, and (*c*) that for the intermediate case, which is the commonest. Case (*a*) applies to the lower alcohols, glycerol, and cane sugar. Measurements cannot be made with these liquids which are miscible with water already. Case (*b*) is that of paraffins, azobenzene, etc.; and case (*c*) is that of aniline, intermediate alcohols, and other substances not completely miscible with water but containing hydroxy-, amino-, and other polar groups. There is a distribution of the added sub-

[36] W. Alexéeff, *Wied. Ann.*, 1886, **28**, 305.
[37] *J. Physical Chem.*, 1930, **34**, 263; *Proc. Roy. Soc.*, 1935, *A*, **148**, 59.
[38] *Bul. Soc. Chim. Români*a, 1930, **12**, 58.
[39] *J. Physical Chem.*, 1932, **36**, 1401.
[40] *Trans. Faraday Soc.*, 1937, **33**, 325.
[41] A. S. C. Lawrence, " Wetting and Detergency," p. 203.

stance between soap and water which is largely in favour of the water in case (a); e.g., some 50% of glycerol is needed to peptise 5% soap. At some stage the consolute temperature of the water and added liquid will fall below that at which the experiments are made. Nicotine has two consolute temperatures and the phase diagram is a ring. Addition of soap reduces the size of the ring until it vanishes at about 8% of sodium stearate at room temperature. Peptisation is attributed to formation of loose complexes between the $-CO_2Na$ group and the polar group of the added peptiser. The difference between the results of McBain and Woo and those of other workers on insoluble substances is explained by the fact that McBain and Woo's water-insoluble dyes (described in their paper only by their trade names) were amines which naturally formed salts with
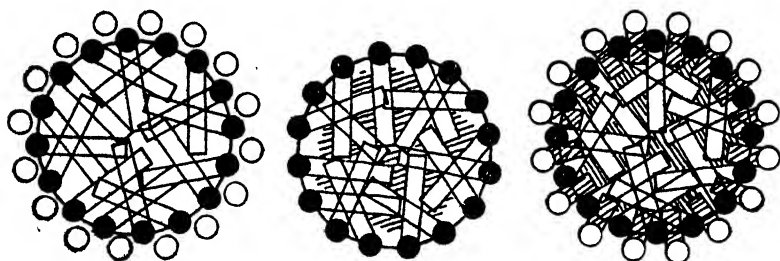
FIG. 1.

(a) *Peptisation alone.*   (b) *Internal solution in the soap micelle.*   (c) *Internal solution and peptisation.*

their soap—laurylsulphonic acid—which dissolved in the water. For instance, yellow AB is 1-benzeneazo-2-naphthylamine, and the BB dye is the tolueneazo-compound.

A. S. C. Lawrence [42] has examined solutions of soaps in the inert solvent, " Nujol." These are interesting in that they are the reverse case of aqueous solutions. The soluble part is now the hydrocarbon chain, while the polar groups are insoluble. Solution does not occur until thermal separation of the polar groups is reached, the temperature for which approaches that of the melting point of the pure soap to isotropic liquid. About this temperature a fluid solution is obtained; below it, the soap solution sets to a gel. At a lower temperature, corresponding with the transition in the soap from plastic to crystalline, the gel is transformed into a paste of micro-crystals. The gel region therefore corresponds with the plastic stage in the soap. Its temperature limits are lowered by addition of polar substances,[43] of which the fatty acids are the most efficient.

[42] *Trans. Faraday Soc.*, 1938, **34**, 660.   [43] *Ibid.*, 1939, **35**, 702.

Calcium and barium soaps are peptised by small amounts of water, which forms fatty acid by hydrolysis. Phenols are also active.

Emulsions.

Discussion of emulsions is frequently complicated by inclusion of very dilute suspensions of oil in water which are stabilised by a charge and not by an emulsifying agent. It is most desirable that the name should be restricted to those systems in which a third substance acts as emulsifier. The dilute suspensions are typical hydrophobic sols. As such they are of special interest since the particles are spheres with a uniform adsorbing surface. Excluding these suspensions, we have the two classes of emulsions—oil in water, and water in oil. In general, particle size is fairly uniform and large, the diameter being from 0·5 to 5μ. G. S. Hartley[44] has attempted a theoretical discussion of particle size and stability, starting from the model of oil dissolved inside the micelle. This treatment suffers, however, from the difficulty that there seems to be no continuity from this model to emulsion droplets. Saturation of the micelle by oil represents an equilibrium. Some abrupt change must occur then, and very much larger droplets become the stable ones in the emulsion. Pickering's experiments,[32] in which there was a large excess of soap available for the micelle swelling through the intermediate stage, show the two processes of internal solution and emulsification proceeding independently and without continuity.

The chief property of emulsions considered hitherto is that of phase inversion. With soaps or similar amphipathic water-soluble substances as emulsifiers, oil-in-water systems are obtained. Addition of salts of calcium, barium, thorium, etc., causes inversion. The wedge [45] theory attempted an explanation on the unsupported and highly improbable idea that the bivalent soap molecules had a wedge form which determined the nature of the emulsion. The simple expedient of using a univalent kation (e.g., silver or thallous) which forms a water-insoluble soap without giving the wedge form disproves this theory, since phase inversion does occur. J. H. Schulman and E. G. Cockbain [46] have investigated this question, using complex formation in the emulsifier layer to alter its nature. Substances which had already been studied in monolayers were chosen as emulsifiers; e.g., cholesterol dissolved in paraffin gives no emulsion when shaken with water, and sodium cetyl sulphate in the water gives a very poor one, but when both substances are present

[44] " Wetting and Detergency," 1937, 153.

[45] P. Finkle, H. D. Draper, and J. H. Hildebrand, J. Amer. Chem. Soc., 1923, 45, 2780.

[46] Trans. Faraday Soc., 1940, 36, 651.

excellent emulsions are formed and their stiffness is proportional to the rigidity of the complex formed in monolayers. The stability of the emulsion prepared with various substances which reacted with monolayers of cholesterol was in the same order as the reactivity.

It appears that, for stable emulsification of oil in water, the oil droplets must be charged (by the emulsifying agent at the interface which also moves the double-layer potential drop further out into the water). The emulsifying layer must be close-packed and consequently the interfacial tension is small. The amount of water-soluble substance present must be greater than that required to form the monolayer, but when a complex-forming substance is added in the oil no such excess is required. The stability of the emulsion is attributed to van der Waals attraction between the non-polar parts of the emulsifying molecules, and is also affected by interaction between the polar groups of complex-forming substances. Further experiments showed that the emulsion type was oil-in-water when the droplets were charged (as with simple amphipathic emulsifier and with some complexes) but water-in-oil when they were uncharged. Phase inversion can be brought about by addition of calcium salts to a sodium soap-stabilised emulsion, and a similar result is found when sodium hydroxide is added until the p_H is 14. Similarly, heptadecylamine-stabilised emulsions are inverted at very low p_H values. It is concluded that water-in-oil emulsions require that the emulsifier layer should be uncharged and that it should possess a considerable rigidity.

The picture of emulsions, although not complete theoretically, is clear. The two types, oil-in-water and water-in-oil, are fundamentally different : the former owe their stability to the charge on the oil droplets, and this charge is due to the ionised layer of emulsifier. Stability will be poor unless this layer is close-packed—either by choosing a suitable substance or by coupling one, which gives only a gaseous film, with a substance which forms a close-packed complex. Such emulsifiers will also lower the interfacial tension at the oil–water interface, but it seems that the actual value of the residual interfacial tension is not a stability-determining factor, and only affects the work required to form the emulsion. J. L. van der Minne [47] remarks that pairs of liquids such as ether–water and phenol–water do not form emulsions in the neighbourhood of their consolute temperature although the interfacial tension is lower here than in most stable emulsions. It should be noted, however, that this failure to form emulsions is perhaps due to mutual solubility. When water is the continuous phase, the charged oil droplets repel one another since the medium is ionised. With oil as continuous

[47] Symposium of Hydrophobic Colloids, Ned. Chem. Ver., 1938, 138.

phase this factor does not operate, since there is no ionic atmosphere around the droplets. It seems that the stability of water-in-oil emulsions is due to rigidity of the emulsifying layer. Against this, the residual interfacial tension is insufficient to pull the droplets into spheres as in oil-in-water systems. Such emulsions, therefore, contain irregular sack-shaped particles of water whose size depends upon the mechanical treatment of the emulsion as opposed to the true equilibrium which may be reached in oil-in-water emulsions.

R. C. Pink [48] has shown that magnesium and calcium oleates, formed by metathesis in inversion of sodium oleate-stabilised emulsions, are hydrated soaps insoluble in both phases. They act as emulsifiers, therefore, as finally divided solids. Van der Minne has examined emulsions stabilised by ferric oxide flocculated from a sol.

A. King and L. N. Mukerjee [49] have measured the rate of hydrolysis of amyl acetate emulsions, using a number of emulsifying agents. The rate was always higher in the emulsions, but the rate per unit area of interface was greatest in the absence of an emulsifier and varied with different emulsifiers.

The Viscosity of Colloidal Systems.

Graham first recognised high viscosity as a characteristic of hydrophilic colloids, and named his volume efflux viscometer a "Colloidoscope." Later, gelation was recognised also as characteristic of such colloids. Still later it was found that many such sols had an anomalous or non-Newtonian viscosity; i.e., the viscosity calculated by the usual equations, which assume Newtonian flow, varied with the rate of flow. At low rates of shear, the value was very large, decreasing then with increasing rate of shear. This anomaly, combined with W. F. Darke, J. W. McBain, and C. S. Salmon's observation [50] that gelation of soap sols was unaccompanied by any change in osmotic pressure or electrical property, led to the idea that anomalous sols were gels too dilute to support themselves under the deforming force of gravity.* It was also found that many sols whose viscosity was anomalous became birefringent when in flow : these were sols in which the particles were rod-shaped. If the rods are themselves birefringent, orientation by flow makes the sol appear birefringent. By a curious muddling of ideas, the orientated arrangement showing flow birefringence was associated with the "structure" causing the viscous anomaly. Meanwhile A. Einstein [51] had published his well-

[48] J., 1938, 1252; 1939, 619.　　　[49] J. Soc. Chem. Ind., 1938, **57**, 431.

[50] Proc. Roy. Soc., 1921, A, **98**, 395.

[51] Ann. Physik, 1906, [iv], **19**, 289.

* This is perpetuated in the German name equivalent to "structure viscosity."

known equation, which is quoted in the text books in the sterile form $\eta_{sol} = \eta(1 + 2\cdot5V)$, where η_{sol} is the viscosity of the sol, η that of the pure dispersion medium and V the total volume of the disperse phase. In other words, the increase of viscosity of the sol due to the colloid particles is proportional to their total volume only.

Much work has been carried out recently upon the flow character-istics of colloids, but the larger part has been concerned with measurements of the flow of pastes and similar complex mixtures in which the "body" is a commercially useful attribute. The science of "rheology" is mainly concerned with such systems and has been summarised in a recent book.[52] At the same time, however, theoretical and ex-perimental investigations have been made of the problem, less complex systems being used, and the results constitute an important advance in our knowledge and perhaps a starting point for the examination of the more complex systems. If we consider the simplest case of spherical particles too large to show Brownian motion and dispersed to a dilution sufficient for absence of any inter-action between the particles, then in flow the velocity gradient rotates the particles. Each is then surrounded by a region of disturbed flow, in which the liquid is travelling in a direction different from that of the stream-line flow of the undisturbed bulk of the dispersion medium. From these considerations Einstein derived his equation. When, however, concentration is increased, complications set in. Fig. 2 shows an idealised picture of the cross-section of a tube through which a suspension is flowing in laminar or telescopic flow. It is clear that, as shown, each particle of volume $\pi d^3/6$ occupies a volume of d^3, so that the concentration is *ca.* 50%.
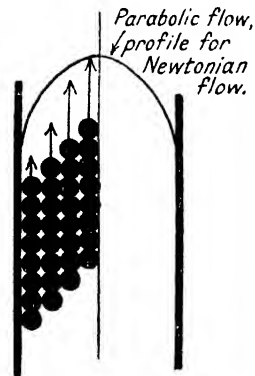
FIG. 2.

Idealised picture of case of laminar flow of paste intake.

In laminar flow each annulus of particles must move with a velocity which increases from zero at the wall to a maximum at the axis of the tube. Shear can take place only across the liquid separating the annuli. In Fig. 2, flow would be vanishingly small and the apparent viscosity very large. Now, according to the Einstein equation there must be no interaction, either directly between the particles or between the regions of disturbed flow around them. Viscosity will therefore have started to increase rapidly above the Einstein value before the stage shown in Fig. 2. When the particles overlap, flow conditions will become more

[52] G. W. Scott Blair, "Industrial Rheology," 1938.

complex still, and the measured viscosity greater. If there are forces of attraction, whether long-range electrical or van der Waals, the paste will have a rigidity and a yield point. It must be recognised that there will be difficulty at high concentrations in distinguishing between real rigidity and very high transference of momentum which will reduce the velocity gradient towards zero and raise the observed viscosity towards infinity. It cannot be urged too strongly that the viscosity of the dispersion medium is unchanged from its normal value. It is the conditions of flow which are disturbed. The rotational movement of the particles and the
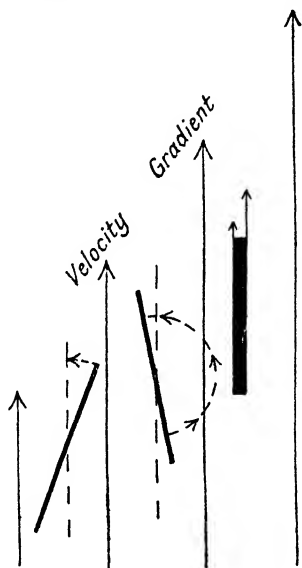
Fig. 3.
Orientation of rods in velocity gradient.

resulting disturbance of flow are sometimes spoken of as an extra dissipation of energy, but it is clearer to regard this as a " sidetracking " of some of the energy which the ordinary equations for calculating viscosity assume to be used only for Newtonian shearing of a homogeneous system.

A spherical particle can have no special orientation with respect to the streamlines of flow. An infinitely thin rod, however, is quite different. When it lies across the velocity gradient, its interference with laminar flow will be greatest, and the velocity gradient will exert a couple upon it which will rotate it until its long axis lies along the streamline (Fig. 3). If it is infinitely thin, it will, in this position, have no effect upon the flow or the viscosity. Particles so

orientated will, however, show their maximum birefringence. This was established first by J. Robinson,[53] who measured viscous anomaly and streaming birefringence in the same apparatus—a coaxial cylinder viscometer with a transparent bottom for the optical observations. Fig. 4, taken from his results for a sol of the tobacco mosaic virus, shows that maximum viscous anomaly is associated with minimum birefringence and *vice versa*. The earlier workers regarded hydrodynamic orientation as irreversible so long as the shearing was continued. This, however, is not so. Rotatory Brownian motion is a disorientating force, and the flow conditions
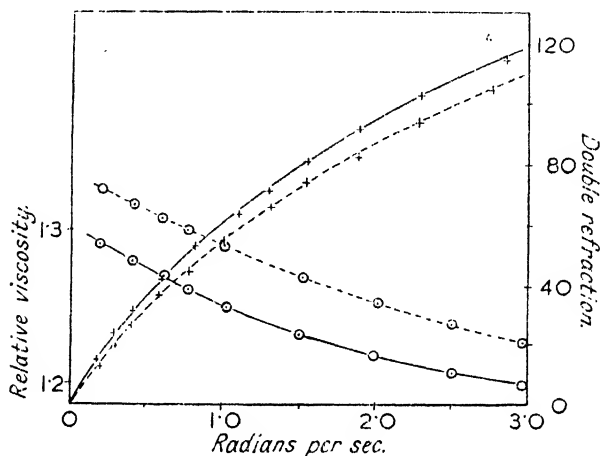
Fig. 4.

0·02% *Tobacco mosaic virus.*

Variation of relative viscosity (○) *and double refraction of flow,* ——— *at* 14·4°, — — — *at* 19·6°, *with rate of shear.*

depend upon the balance of the two forces. Brownian motion will cause a rotational diffusion of rods. If there is any orientation, *i.e.*, more in one position than in any other, then there will be more diffusion away from the position of orientation because there are more particles there. Now, particles diffusing clockwise will tend to be restored to their original position (Fig. 3) by hydrodynamic orientation, but those moving counter-clockwise will have their movement accelerated and will perform a complete rotation. The position at which angular velocity is at a minimum will contain more particles at any moment and will therefore be the observed direction of orientation. This will move in a clockwise sense with increase of rate of shear. The intensity of the birefringence also increases with

[53] *Proc. Roy. Soc.*, 1939, *A*, **170**, 519; also A. S. C. Lawrence, *ibid.*, 1937, *A*, **163**, 323.

rate of shear. We can see that reduction of size of rods or rise of temperature increases disorientation at any fixed rate of shear and *vice versa*. It is noteworthy that rise of temperature increases the disorder and therefore *increases the viscous anomaly*. The viscosity of the dispersion medium retains its normal negative temperature coefficient which may be larger than the increase of viscous anomaly, but, if the comparison is made between viscosities relative to those of the solvent at the temperatures chosen, then the increase of anomaly is shown. Robinson has verified this surprising conclusion.

Several theoretical treatments of the high viscosity of suspensions of rod-shaped particles have been attempted. W. Kuhn [54] and M. L. Huggins [55] have shown that the viscosity will depend upon the particle shape, but they assume random orientation and so fail to explain viscous anomaly. Most of the experimental workers have assumed complete orientation. This is only true when the particles are very large and elongated, *i.e.*, when Brownian disorientation is negligible compared with hydrodynamic orientation. For example, X-ray examination of such suspensions in flow has shown that there is almost complete orientation.[56] E. Guth [57] and P. Boeder [58] have given theoretical treatment on the lines discussed above but failed to calculate the additional dissipation of energy due to the precessional motion of the rods. Robinson surmounted this difficulty by using the optical data which give both the number orientated and their direction * with respect to the streamlines. As already mentioned, the orientation is statistical—the preferred position is that through which the particles pass most slowly. The actual motion of a rod-shaped particle is precessional owing to its rotation in the velocity gradient plus its linear flow along the streamlines. From the experimental data for the orientation, the rate of dissipation of energy has been calculated, and the apparent viscosity of the sol so obtained is in good agreement with the experimental values.

This work has not been extended to the very important systems in which the particles are not rigid, *e.g.*, polymers. This problem is complicated by the non-linear form of chemically linear polymer molecules. As Kuhn has shown, a velocity gradient imposes a tension on an anisodimensional particle. An aperiodically coiled polymer molecule will therefore be pulled out as well as rotated.

[54] *Z. physikal. Chem.*, 1932, *A*, **161**, 1, 427.

[55] *J. Appl. Physics*, 1939, **10**, 700.

[56] K. Hess and J. Gundermann, *Ber.*, 1937, **70**, 1800; K. Hess, H. Kiessig, and W. Philippoff, *Naturwiss.*, 1938, **26**, 184.

[57] *Kolloid-Z.*, 1936, **74**, 147; **75**, 15.   [58] *Z. Physik*, 1932, **75**, 259.

* More exactly, that of the optic axis, but in the cases chosen it coincided with the long geometrical axes of the rods.

When, however, its long axis lies along the streamline, it will tend to coil up again. During these complex movements it will carry with it a certain amount of the dispersion medium immobilised inside the coil. Shear may cause strain birefringence, and the straightened out particles may then show orientation birefringence. The observations of A. von Muralt and J. T. Edsall [59] on myosin sols showed the two effects in the same sol, the strain birefringence occurring in the less highly sheared part, which behaved like a weak gel, while the more highly sheared part was fluid and showed the orientation effect.

The general and very important conclusion is that viscous anomaly is the result of interference with the normal laminar flow of the solvent by the precessional motion of the particles. The viscosity is anomalous (*i.e.*, it varies with the rate of shear) because the interference depends upon the balance of hydrodynamic orientation and Brownian disorientation. Other conditions being unchanged, variations of rate of shear alter the hydrodynamic orientation. Further complexities are introduced when there is mutual interference between the particles, either *via* the dispersion medium or by direct adhesion. The consequences of interference and the resulting phenomena have not been recognised sufficiently by workers on this subject. The need for working at low concentrations has been ignored, especially by the rheologists.

C. F. Goodeve [60] has proposed a theory of anomalous viscosity and thixotropy based upon particle adhesion, the flow properties of the system being determined by the rate of breaking and remaking these links. This theory is obviously inadequate to explain the type of viscous anomaly described above, where there is no mutual interaction at all, but it would seem to be of particular value as applied to pastes. The experimental evidence from the better-known thixotropic systems shows that the rate of re-formation of links is quite slow compared with the rate of breaking. He concludes that such systems have a " scaffolding " structure. This name seems unfortunate, since it suggests some sort of cubic lattice-like structure rather than the picture of a random mesh which has been accepted for many years.

Gelation and Thixotropy.

The confusion already mentioned between anomalous viscosity and gelation makes it necessary to discuss the latter before summarising the position. All gelation is due to a reduction of the solubility of the solute : by cooling sols of hydrophilic colloids and by addition of electrolytes to hydrophobic ones in amounts less than those

[59] *J. Biol. Chem.*, 1930, **89**, 289, 315; *Trans. Faraday Soc.*, 1930, **26**, 837.
[60] *Ibid.*, 1939, **35**, 342.

required for coagulation. In a few cases, *e.g.*, soaps, the gel stage can also be reached by warming the less soluble curd fibre phase in water. This is important in so far as it shows that the gel stage is not merely a metastable system. Thixotropic gels, which have received the most attention recently (partly because they are most amenable to experimental investigation), are gels which are broken down easily to fluids by shaking and reset on standing for a short time. Attempts have been made to explain thixotropy by the peculiar electrical conditions (cf. p. 102). H. Freundlich,[61] H. C. Hamaker,[3] I. Langmuir,[62] and S. Levine [4] have tried to explain thixotropy by means of the potential curves for charged particles. This method, however, is unsatisfactory for two main reasons. First, it does not explain the resetting after a time lag; and, secondly, it fails to explain that thixotropy is usually a phenomenon due to non-spherical particles. For example, alumina sols show no thixotropy when prepared by precipitation and subsequent peptisation. When, however, prepared by Crum Brown's method of boiling the basic acetate with water, the sol is thixotropic. In the former case the particles are spherical; in the latter, they are thin crystalline plates. It may be that this criticism is due to the quite fortuitous fact that the maximum concentrations of spherical particles attainable in true hydrophobic sols are too small for a continuous structure to be built up, whereas filamentary or plate-shaped particles can build such a structure. On the other hand, the criticism may be real on the grounds that the partial coagulation required for thixotropic gelation results from discharging parts of the surfaces of the rods or plates leaving the remainder charged—a position not recognised in the potential-curve theories. If this were the case, the locally discharged patches would adhere to similar patches in other particles and a continuous structure could be built up provided that the particles were themselves fairly large. A. I. Rabinerson [63] distinguishes between sols in which the particles have their ζ potential generally lowered, and those where it is lowered at points only. In the first case, aggregation is compact, and in the latter extended. We may, however, consider first the gelation process without any reference to the nature of the forces of adhesion, merely making the reservation that an elastic gel does require adhesion at the points of contact in the mesh structure of particles whatever their shape may be. Certain facts must be recognised. Gels are optically anisotropic. Thixotropic gels are being sheared when broken down to fluid by shaking. This clearly implies orientation of the anisodimensional particles. Examination of the gelation in polarised light reveals

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[61] "Thixotropy," 1935, p. 13.   [62] *J. Chem. Physics*, 1938, **6**, 873.
[63] *Acta Physicochim. U.R.S.S.*, 1938, **8**, 733.

this clearly. On re-setting, the flow birefringence in the sol, and therefore the arrangement of particles in groups each with common orientation, is destroyed. This observation is in complete agreement with the anomalous viscosity of sols of anisodimensional particles described above, and a further connection is found in the temperature effect. Rate of gelation *increases* with temperature provided that there be no solubility change. In the soaps, of course, there is a marked solubility change, and K. H. Meyer and A. van der Wijk [64] have suggested that gelation of gelatin is also due to a sudden change of solubility. Where there is no such change of solubility, as in the thixotropic systems, the temperature effect has been confirmed. N. Sata and N. Naruse [65] have observed the effect in alumina sols. M. Prasad and D. M. Desai [66] have also observed it in complex inorganic systems. Bentonite also shows the effect.[67] I. Langmuir [68] has measured the rate of disappearance of streaming birefringence in bentonite sols as a function of temperature, and has found that the time decreases as temperature rises. He pointed out that the loss of birefringence is due to rotational Brownian motion. Using the rotational diffusion equation and the temperature coefficient of the rate of loss of birefringence, he calculated the energy of activation, but, at the lowest concentration used by him, two-thirds of this is due to the change of viscosity of the water. The Einstein equation for the Brownian rotation (of spheres) is $\theta^2 = KTt/4\pi r^3\eta$, where θ is the average angle moved through in the time t, r is the radius of the particles, and η the viscosity of the dispersion medium at the absolute temperature T. The energy barrier appeared at a concentration of 1·4%. Langmuir developed a theory which required the particles, which are thin plates, to be orientated in a pseudo-cubic lattice and held in position by long-range electrical forces of adhesion. Although this distance is large, *viz.*, 5000 A., it is not large compared with the size of the plates, which have a diameter of 4500 A. If we calculate the volume filled by these discs rotating, we get an effective volume filled which brings them into contact at about 3%. From the criterion of touching at points, the effective volume will be d^3 instead of $\pi d^3/6$. This brings the critical concentration above which the particles are not free to rotate to *ca.* 1·5%. The effective volume is obviously less than d^3 but will be somewhat increased again by addition of the field of disturbed flow around the particles. This correction, however,

[64] *Helv. Chim. Acta,* 1937, **20,** 1331.   [65] *Kolloid-Z.,* 1939, **86,** 102.

[66] *J. Indian Chem. Soc.,* 1939, **16,** 117.

[67] E. A. Hauser and C. E. Reed, *J. Physical Chem.,* 1936, **40,** 1169; 1937, **41,** 911; E. A. Hauser and D. S. le Beau, *Kolloid-Z.,* 1939, **86,** 105.

[68] *J. Chem. Physics,* 1938, **6,** 873.

will not be large.   Langmuir observed experimentally 1·4% as the critical concentration.   It seems probable, therefore, that the energy barrier is simply due to interference with Brownian disorientation and that, in sufficiently dilute sols, the whole of the temperature coefficient would be covered by the change of viscosity of the water.   Hence it seems that Langmuir's results are explicable on the random-mesh theory of gel structure.   This explanation also explains the anisotropy of the gel, whereas Langmuir's pictured gel should have a birefringence which is the sum of the individual birefringences of the orientated particles.   It has been suggested that such gels might be micro-crystalline [69] and therefore effectively isotropic, but such a picture fails to explain adhesion of the micro-crystalline units.   Incidentally, working on bentonite suspensions, Hauser [67] has experimentally confirmed the disorientation theory of gelation.

The phenomenon of " rheopexy " [70] is also explicable on the same lines.   Rheopexy is the increased rate of resetting of a thixotropic gel as a result of gentle motion—rolling a test-tube of the liquid gently backwards and forwards between the hands.   It is clear that such a movement is one which causes mild turbulence and is a disorientating one and not a steady shearing.   It is therefore an addition to the disorientating action of rotatory Brownian motion.

When the particles are flexible, the picture becomes more complex. The breakdown of a felted mass of intertwined fibrils, whether adhering at points of contact or not, is obviously very much more difficult than the corresponding case of rigid rods.   A reduction of apparent viscosity by continued shearing has been observed in gelatin solutions.[71]   In these cases, it is particularly important that the limitations of the Ostwald or other volume efflux viscometers should be realised.   If the system takes an appreciable time to reach steady flow, it will have passed through the instrument long before this steady state is reached.   Table II gives a survey of possible cases.

True emulsions are not included in this table, since they show a peculiar anomaly due to distortion of the droplets and work is done against the interfacial tension.   The size distribution is also altered. This, incidentally, is the principle of the homogeniser, which applies a very high rate of shear to the emulsion either by forcing it through a small orifice or by shearing between two plates close together and rotating in opposite directions at high speed.   Rigidity of particles

[69] *Trans. Faraday Soc.*, 1940, **36**, 730.
[70] H. Freundlich and F. Juliusburger, *ibid.*, 1935, **31**, 920.
[71] B. Kandelaki, G. Kikodze, and N. Dolidze, *J. Phys. Chem. Russ.*, 1937, **10**, 524.

TABLE II.

| Particles. | Examples. | Behaviour under shear. | |
		Dilute sols.	Concentrated sols.
Spherical	Oil hydrosols	Einstein's case	Plastic pastes
Nearly isodimensional	Au, C, clay sols	Einstein constant [72] abnormally large; flow Newtonian or slightly anomalous	,, ,,
Anisodimensional.			
Flexible fibrils	Gelatin, agar, soaps, polymers	Possible orientation with degradation	Gelation or high viscosity
Rigid rods	Benzopurpurin V_2O_5, tobacco virus, Hg sulphosalicylic acid	Hydrodynamic orientation	Thixotropic gels
Rigid plates	Fe_2O_3, Al_2O_3, bentonite	,, ,,	,, ,,

is defined as rigidity sufficient to withstand deformation by Brownian motion. Rigid rods then rotate, whereas flexible ones are distorted. Benzopurpurin forms thin crystalline needles which can be seen under the ultra-microscope to be partially flexible. Before this table can be regarded as an accurate scheme, it is necessary to relate the size factor with viscous behaviour, and also to define concentration in an entirely new manner.

Size Factor.—As we have seen, the behaviour of anisodimensional particles is determined by the balance between hydrodynamic orientating forces and rotational Brownian disorientation. The Reynolds number gives the upper limit to which the rate of flow can be increased without turbulence setting in. It follows, therefore, that particles below a certain size and length/breadth ratio cannot be orientated by flow,[73] but the viscosity of their sols will be larger than those of spherical particles of similar size. The flow will be Newtonian, but the Einstein factor will be unduly large. Huggins has discussed the viscosity in the homologous series of fatty acids. When particles are so large that Brownian disorientation is negligible, a new disorientating factor appears. The finite cross-section of the rods is itself a source of instability, since one side tends to move faster than the other. There is, therefore, still a torque which, in one sense, causes precession. In this connection, it is well known that rods falling through a liquid at rest deviate from a straight-line path. J. W. McBain and (Mrs.) M. E. L. McBain [74] have carried out an ingenious experiment in which rates of sedimentation

[72] E. W. J. Mardles, *Trans. Faraday Soc.*, 1940, **36**, 1007.

[73] A. Peterlin, *Z. Physik*, 1938, **111**, 232; *Kolloid-Z.*, 1939, **38**, 230.

[74] *J. Amer. Chem. Soc.*, 1937, **59**, 342.

of fibrils of quartz, and of the spheres formed by fusing the fibrils, were measured in water. Great elongation in the fibrils caused only a 13-fold increase of viscous resistance. The authors concluded that the high viscosity of suspensions cannot be due to length alone. This explanation is obviously incorrect. The particles are falling through a fluid across which there is no velocity gradient. There is still a shape effect, but not approaching that found in viscosity measurements where the particles increase the viscosity by their precessional motion which, as we have seen, requires the velocity gradient. McBain and McBain's case is similar to the conditions in the ultracentrifuge.

H. G. F. Winkler [75] has found thixotropy in suspensions in water and organic liquids of non-spherical mineral particles of microscopic size. Spherical particles, however, showed no thixotropy. E. A. Hauser and D. S. Le Beau [76] have measured the viscosity of suspensions of fractionated montmorillonite and bentonite and found that at very low concentrations the value decreases with increasing particle size. They attribute the high viscosity of the finest sols to hydration, but it is possible that the increased Brownian disorientation with decreasing size is sufficient to explain these results. S. A. Glickman [77] detected anomaly at low rates of shear in sols of cellulose nitrate. The critical stress for disappearance of anomaly fell with increase of particle size. Roughly, we may say that (with a given concentration) the viscosity will rise to a maximum with increase of particle size and then decrease again. The changes of viscosity of any system will then obviously depend upon the original position on the curve of the starting material.

Degradation of particles by shear is important. Two different types of degradation must be recognised—breaking long ones into shorter lengths, and breaking down bundles of particles which may be in a nematic or para-crystalline arrangement, i.e., with long axes parallel but with no other regularity. Again, the starting point determines whether breakdown increases or decreases the viscosity. R. Signer [78] has observed degradation of polymer molecules at very high rates of shear. Soap solutions probably show degradation of the second kind, but it should be noted that formation of gel is a quite separate case. E. Heymann [79] has shown that the sol–gel change in sodium oleate–water systems is unaccompanied by any volume change. This is not surprising, however, if we regard gelation as the linking of particles already present in the sol (and possibly increasing in number) and not as any change in the packing of the

[75] *Kolloid-Beih.*, 1938, **48**, 341.   [76] *Kolloid-Z.*, 1939, **86**, 105.
[77] *J. Phys. Chem. Russ.*, 1938, **11**, 825.
[78] *Helv. Chim. Acta*, 1936, **19**, 1324.   [79] *Trans. Faraday Soc.*, 1938, **34**, 689.

molecules in the micelles.   M. Ulmann,[80] however, has found that the specific volumes of this soap fall into three well-defined regions with transitions at 0·03% and at 0·9%.

Effective Volume and Concentration.—The picture of the precessional motion of an anisodimensional particle in a velocity gradient will be in three dimensions a sort of solid double cone.   Now, it is clear that some concentration will be reached at which the total volume effectively filled by these solid cones will be equal to the total volume of the solution.   Further increase of concentration will cause interference, higher transmission of momentum, and much higher viscosity.   The hydrodynamic analysis of the results will no longer be accurate.   The longer the particles, the lower will be the critical concentration.   It is clear that the effective volume will be less than $\pi l^3/6$, where l is the length of the rod, but greater than $\pi(\frac{1}{2}l)^2\theta$, which is H. Staudinger's assumed value, θ being the thickness.   It is also clear that this critical concentration will vary with the rate of shear.   With complete orientation, for example, the effective volume has fallen to the actual volume.   Staudinger assumed, however, that his " limiting " concentration was constant.   He used Ostwald viscometers in which rate of shear and therefore critical concentration varied continuously across the tube.   Similarly, a system of anisodimensional particles at rest will retain streaming birefringence permanently unless the particles have sufficient space to disorientate themselves under Brownian motion. The relation between the latter critical concentration (which is not a completely abrupt change) and the critical concentration in flow will not be definite, since the latter is not a constant at all.   Nevertheless, it is of the greatest importance that its significance should be realised—namely, that all measurements of viscosity of solutions of anisodimensional particles should be made below it.   Slightly above it, the overlapping of the particle volumes is shown by a very large deflection on setting the Couette viscometer in motion.   The deflection then falls and reaches a steady value.   If, with a sol of this concentration, the outer cylinder is rotated by hand through a few degrees, the inner (hanging) one follows as if linked rigidly.   On standing, however, the hanging cylinder gradually returns to rest during some hours.   From the rate of return, viscosities can be measured at rates of shear as low as one revolution of the outer cylinder in six months.   The return shows that the sol is liquid, but with a velocity gradient so small that its viscosity approaches infinity. The rate of return may be compared with Maxwell's relaxation time.

Only in the case of the larger polymer molecules is anomalous viscosity observed.   Below a molecular weight of 100,000, flow is

          [80] *Z. physikal. Chem.*, 1938, **182**, 18.

Newtonian and sometimes remains so to even higher values.[81] Flow birefringence has been observed at much lower values,[82] *e.g.*, in a polystyrene of molecular weight 5000, but the orientation of such particles was only slightly different from random orientation. Not until the molecular weight rises above 50,000 does serious orientation begin. At 630,000 the angle of isocline has only reached *ca.* 75° (random orientation gives 45°, and complete orientation 90°). Signer explains his results by a partially coiled form. Increasing the rate of shear tends to straighten these, and the observed flow birefringence increases more rapidly than required by the simple orientation theory as developed for rigid rods.[82, 83] Signer's results for polystyrenes and cellulose nitrate solutions support the hydrodynamical treatment of anomalous viscosity, and he rejects Kuhn's theory. For Newtonian solutions, the Staudinger equation is generally accepted as giving results of the correct order of magnitude, but his attempt to justify it on hydrodynamical grounds is open to serious criticism. G. Gee [84] has shown that molecular weights of fractionated crepe rubber determined by the Staudinger viscosity method agree well with those obtained by osmotic pressure measurements from values of 60,000 to 350,000.

In the Second Report of the Academy of Sciences of Amsterdam on Viscosity and Plasticity, J. M. Burgers [85] summarises the work on the viscosity of suspensions of small particles of elongated form. He concludes that Staudinger's formula is an approximation to one of the theoretical formulæ, but it is clear that no general formula has yet been found. It is generally agreed also that the results for polymer molecules, especially those of higher molecular weight, can be explained only by some assumptions of deformation. The complexity of the position in this respect has already been indicated. It may be noted, however, that combination of temperature effects upon viscous and optical streaming properties may provide an experimental approach.[86] It is apparently satisfactory to apply hydrodynamical treatment. This is not surprising in the case of the large rigid rods in thixotropic systems, and it is easy to understand in the case of polymers on account of the very close association of the solvent with the surface of the polymer particle.[87] It may be

[81] Staudinger, " Die hochmolekularen organischen Verbindungen," 1932, p. 188.

[82] R. Signer and C. Sadron, *Helv. Chim. Acta*, 1936, **19**, 1324.

[83] R. Signer and P. von Tavel, *ibid.*, 1938, **21**, 535.

[84] *Trans. Faraday Soc.*, 1940, **36**, 1163.

[85] P. 113 *et seq.* Both this summary and the main report are very important and should be consulted.

[86] A. S. C. Lawrence, *loc. cit.*, ref. (53).

[87] Cf. J. N. Brønsted and K. Volqvartz, *Trans. Faraday Soc.*, 1940, **36**, 619.

noted that the most important assumption underlying the hydro-dynamic treatment is that there shall be no slip at the solvent–particle interface.

In the above-mentioned report C. J. van Nieuwenburg remarks that, although much experimental work has been carried out in measuring the plastic properties of various materials, the greater number of the instruments used do not allow an unambiguous relation between rate of shear and shearing stress; further, that measurement of " plasticity " cannot be expected to yield useful results unless plasticity is itself defined and complications due to other properties allowed for or avoided, e.g., elasticity, thixotropy, wall slip, etc.

Finally, it cannot be emphasised too strongly that the investig-ation of flow properties should be carried out in a suitable viscometer. Where viscous anomaly exists, it has been pointed out that the Ost-wald type is unsatisfactory since the sol is moving with different viscosities in different parts of the tube. The same criticism applies to observations of streaming birefringence in flow through a tube. Some workers, however, have used the Couette instrument for the optical work and the Ostwald for viscosity and then compared the results. Even in the absence of anomaly, the Ostwald type is not entirely satisfactory, since the theoretical treatment requires the absence of inertia effects (connected with the accelerations or decelerations of particles or elements of volume of the liquid). It has been shown that the Couette viscometer gives confirmation of the Einstein equation, whereas the Ostwald gave values slightly too low.[88] For transparent solutions, A. S. C. Lawrence's coaxial cylinder instrument [89] is the most satisfactory. For plastic pastes, C. F. Goodeve [90] has described an ingenious instrument in which the rate of shear is varied by alteration of the spacing of two truncated cones which take the place of the orthodox cylinders. J. Pryce-Jones [91] has described an important " thixotrometer " with which he has examined the characteristics of paints.

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[88] F. Eirich and O. Goldschmid, Kolloid-Z., 1937, 81, 7.
[89] See J. Robinson, loc. cit., ref. (53).
[90] J. Sci. Instr., 1939, 16, 19.
[91] J. Oil Colour Chem. Assoc., 1936, 295.

INORGANIC CHEMISTRY.

1. Introduction and General.

During the year under review there has been a steady flow of publications covering very many topics in inorganic chemistry. In spite of the comparatively large volume of published work, however, it has proved a difficult task to select any special contributions as constituting outstanding advances. The year has witnessed rather a general advance, made up of small additions to our knowledge here and there, of the continuation of systematic experimental studies which have been in progress for some time, and of the fuller utilisation of special technique.

In this Report brief summaries of a number of diverse experimental papers covering practically the whole of the Periodic Table are included in the first section. No systematic account is given, however, of recent publications on complex salts, nor has the very wide subject of heterogeneous equilibria been considered. In each of these fields the inaccessibility of certain publications would have greatly impeded the preparation of a satisfactory survey. Subsequent sections of the Report deal with the boron hydrides, with the fluorination of inorganic compounds, and with the thermal diffusion method of isotope separation. The review of these topics was thought to be timely, for in each instance a considerable volume of important experimental material had accumulated, which had not, as far as the Reporters were aware, been summarised in recent publications.

A method of preparing pure deuterium peroxide has been described [1] in which deuterium oxide vapour is blown through a mixture of deuterosulphuric acid and potassium persulphate at 70—90°. The operation is conducted in an all-glass apparatus and the mixture of D_2O and D_2O_2 formed is fractionally condensed and further enriched in D_2O_2 by fractional distillation. The dilute peroxide solution resulting is again sent through the acid mixture, and the cycle of operations repeated until 100% D_2O_2 is obtained. The compound HDO_2 is synthesised from equimolecular quantities of H_2O_2 and D_2O_2. The method is stated to be suitable also for the preparation of H_2O_2 of high purity.

A further contribution to the controversial subject of lead suboxide has been made by L. L. Bircumshaw and I. Harris.[2] Accurate

[1] F. Feher, *Ber.*, 1939, **72**, 1789.   [2] *J.*, 1939, 1637.

analyses were made of the gases evolved when lead oxalate is decomposed in a vacuum at 300°. These indicate that the reaction is represented by the equation $3PbC_2O_4 \longrightarrow 2PbO + Pb + 4CO_2 + 2CO$, and that lead sub-oxide is not formed. This conclusion is supported by X-ray photographs of the residue and by measurements of its electrical conductivity, from which it appears that the grey-black powder is an intimate mixture of lead and the red tetragonal form of lead monoxide.

New thiobasic mercury salts have been described. The compound $Hg(HgS)SO_4$ is prepared from mercuric sulphide by mixing it with equal parts of perhydrol and concentrated sulphuric acid, warming until the reaction product is white, and pouring into water.[3] It is shown that $Hg(HgS)SO_4$ gives a characteristic X-ray diagram, and is not a mixture of sulphide and sulphate. The second compound [4] has the formula $Hg_3S_2Cr_2O_7$, and is prepared by heating freshly precipitated mercuric sulphide on a water-bath with an aqueous solution of chromium trioxide. Here again, the X-ray diagram is that of a new substance, the structure assigned to which is $[Hg(HgS)_2]Cr_2O_7$.

The dielectric constant of aluminium bromide has been measured,[5] and it has been shown that the dipole moment is zero for the liquid and for its solutions in bromine, carbon disulphide, or benzene. These results indicate the existence of symmetrical Al_2Br_6 molecules under the above conditions. Measurements by I. Poppick and A. Lehrman [6] of the parachor of this compound in benzene solution show that the molecular complexity is the same in solution as in the molten state. Products containing approximately 75% of anhydrous aluminium perchlorate have been obtained by the action of anhydrous perchloric acid on pure aluminium chloride, followed by evaporation of unchanged acid and sublimation of unchanged chloride.[7] It was shown that aluminium could not be deposited from solutions of the perchlorate in organic solvents.

Cyanates of silicon, phosphorus, and boron are described by G. S. Forbes and H. H. Anderson.[8] Silicon tetrachloride reacted on refluxing with a suspension of silver (iso)cyanate in benzene, 98% of the product consisting of $Si(NCO)_4$ (m. p. 26·0°, b. p. 185·6°) and the remainder of $Si(OCN)_4$ (m. p. 34·5°, b. p. 247·2°). The identification of these compounds rested on analogies with ethyl

[3] G. L. Chabovski and E. Potavian, *Bul. Chim. Soc. Române*, 1938, **39**, 27.
[4] G. L. Chabovski and T. Trifǎrescu, *ibid.*, p. 65.
[5] V. A. Plotnikov, I. A. Scheka, and Z. A. Jankelevitsch, *J. Gen. Chem. Russia*, 1939, **9**, 868.
[6] *J. Amer. Chem. Soc.*, 1939, **61**, 3237.
[7] E. G. Hackenberg and H. Ulich, *Z. anorg. Chem.*, 1939, **243**, 99.
[8] *J. Amer. Chem. Soc.*, 1940, **62**, 761.

*iso*cyanate and cyanate.   Phosphorus trichloride yielded $P(NCO)_3$ (m. p. $- 2\cdot0°$, b. p. $169\cdot3°$) as the only volatile product, and boron trichloride yielded a white solid of low solubility which decomposed on moderate heating and, from its analysis and properties, was taken to be $B(OCN)_3$.   These authors describe unsuccessful attempts to prepare boron chlorobromides, fluorobromides, oxychloride, and oxybromide.

Interesting new addition products of boron trifluoride with sulphates and phosphates are described by P. Baumgarten and H. Hennig.[9]   Potassium sulphate absorbs boron trifluoride at about 300° and forms the compound K_2SO_4,BF_3; further addition of the trifluoride to this compound occurs with some difficulty, and absorption ceases before the composition $K_2SO_4,2BF_3$ is reached. Cæsium sulphate readily forms $Cs_2SO_4,2BF_3$ at 250—300°, but Na_2SO_4,BF_3 is obtained with difficulty at 310—330°.   Lithium sulphate absorbs very little boron trifluoride, and the alkaline-earth sulphates are indifferent, although thallous sulphate yields Tl_2SO_4,BF_3.   These sulphate–borofluorides are regarded as true additive compounds.   All evolve boron trifluoride when heated, and are immediately decomposed by water into the sulphate and boron trifluoride, which is further hydrolysed to boric and fluoboric acids.   As in the similar series of additive compounds of sulphur trioxide, combination between a sulphate and boron trifluoride probably occurs by completion of the boron electron octet with a lone pair of electrons from an oxygen atom in the sulphate ion. Analogous compounds, $K_4P_2O_7,4BF_3$ and $K_3PO_4,3BF_3$, are formed from boron trifluoride and potassium pyro- and ortho-phosphate, respectively, at about 400°; the sodium salts yield similar products. Under similar conditions sulphur trioxide gives no additive compounds, but decomposes the phosphates.

Indications have been obtained of the formation of a boron oxy-fluoride, $(BOF)_3$, in the reaction between boron trifluoride and trioxide at 100—340°.[10]   The supposed oxyfluoride is stable in the gaseous state at these temperatures, but on cooling, it decomposes rapidly with deposition of an unidentified colourless solid.   The oxyfluoride is also stated to be a primary product of the reaction of boron trifluoride with certain salts of oxy-acids; with potassium orthoborate, nitrate, and carbonate the changes are represented by the following equations : $3KBO_2 + 6BF_3 = 3KBF_4 + 2(BOF)_3$; $6KNO_3 + 9BF_3 = 6KBF_4 + (BOF)_3 + 3N_2O_5$; $3K_2CO_3 + 9BF_3 = 6KBF_4 + (BOF)_3 + 3CO_2$.   Similar reactions occur with alkaline-earth salts, except that metallic fluorides are the final solid products.

[9] *Ber.*, 1939, **72**, 1743.
[10] P. Baumgarten and W. Bruns, *ibid.*, p. 1753.

Magnesium oxide reacts thus : $3MgO + 3BF_3 = 3MgF_2 + (BOF)_3$. A similar reaction occurs with calcium oxide, but less readily.

During the past year the chemistry of the rare-earth elements has again attracted considerable attention. J. Ant-Wuorinen [11] has described a method of separating these elements by fractional hydrolysis of aqueous solutions of their azides, which is effected electrolytically in a diaphragm cell with platinum electrodes. G. Mannelli [12] has found that all the rare-earth metals can be precipitated quantitatively as their 8-hydroxyquinoline compounds, and that the differences of p_H necessary for precipitation of cerium, thorium, and yttrium enable these elements to be separated from a crude rare-earth mixture. The electrolytic separation of cerium as ceric phosphate [13] has been improved by I. A. Atanasiu and M. Babor [14] and rendered suitable for direct application to a sulphuric acid extract of monazite; in a supplementary paper [15] these authors have described the preparation and properties of hydrated and anhydrous ceric phosphate.

The preparation and study of pure compounds of individual members of the rare-earth group have been continued; W. Feit [16] has obtained pure holmium compounds by fractional crystallisation of rare-earth bromates and basic nitrates, and H. Bommer [17] has examined the crystal structure of metallic holmium, which has a hexagonal close-packed lattice ($a = 3 \cdot 557$ A., $c = 5 \cdot 620$ A.; $d = 8 \cdot 764$; at. vol. $= 18 \cdot 65$ c.c.). Magnetic measurements by Bommer show that holmium obeys the Curie–Weiss law at 90—515° K. The calculated magnetic moment is $10 \cdot 6$ Bohr magnetons. The purification of gadolinium from traces of europium, which is reduced to the bivalent state with strontium amalgam, is also described.[18] New compounds of the rare earths include mesoperiodates of yttrium, cerium, and erbium of the type $MIO_5,4H_2O$, and a hydrated diorthoperiodate of yttrium, $Y_4I_2O_{13},11H_2O$.[19]

Continued interest in the recently-developed chemistry of gallium is shown by a paper dealing with the chlorides. A. W. Laubengayer and F. B. Schirmer [20] have prepared $GaCl_3$ and $GaCl_2$ in a state of purity and measured the vapour pressures and vapour densities over wide temperature ranges. The trichloride, prepared by passing chlorine, diluted with nitrogen, over heated gallium,

[11] *Suomen Kem.*, 1940, **13**, *B*, 1.

[12] *Atti X Congr. intern. Chim.*, 1938, II, 718.

[13] J. W. Neckers and H. C. Kremers, *J. Amer. Chem. Soc.*, 1928, **50**, 955.

[14] *Bull. Acad. Sci. Roumaine*, 1939, **20**, 27.   [15] *Ibid.*, p. 32.

[16] *Z. anorg. Chem.*, 1940, **243**, 276.   [17] *Ibid.*, 1939, **242**, 277.

[18] L. Rolla, *Atti X Congr. intern. Chim.*, 1938, II, 766.

[19] R. K. Bahl and S. Singh, *J. Indian Chem. Soc.*, 1939, **16**, 375.

[20] *J. Amer. Chem. Soc.*, 1940, **62**, 1578.

melts at $77 \cdot 0°$ and boils at $200 \cdot 0°/760$ mm.; below $200°$ its vapour consists chiefly of Ga_2Cl_6 molecules, but the degree of dissociation into $GaCl_3$ increases from $3 \cdot 44\%$ at $205 \cdot 5°$ to $88 \cdot 26\%$ at $498 \cdot 3°$. The dichloride was prepared by heating the trichloride with excess of gallium in a vacuum at $175°$, and distilling off the product at $225°$. Traces of the trichloride formed by decomposition were subsequently removed by distillation at $160°$. The lower chloride forms apparently dimorphous, colourless crystals which melt at $170 \cdot 5°$, and slowly decompose into the trichloride and gallium above $200°$. Although the diamagnetism of the solid [21] suggests that it is composed of Ga_2Cl_4 molecules, the vapour at 400—$470°$ contains an appreciable proportion of $GaCl_2$, in which gallium exhibits anomalous bivalency. No evidence was obtained of the existence of the monochloride, $GaCl$.

Metallic carbonyls have been further studied. H. Schulten [22] reports the production of rhenium halogeno-pentacarbonyls, $Re(CO)_5X$, where $X = Cl$, Br, or I. These are obtained when K_2ReX_6 or other rhenium halogen compounds are heated in carbon monoxide at $230°/200$ atm. They are stable in air and insoluble in water, but will dissolve in organic solvents and may be sublimed in an atmosphere of carbon monoxide. The same author has studied the preparation of $[Co(CO)_4]_2$ from anhydrous cobalt halides and carbon monoxide.[23] The reaction occurs most easily with the iodide, less so with the bromide and chloride, and not at all with the fluoride. Cobalt iodide and carbon monoxide react at 200 atm. even at room temperature, and the resulting addition compound CoI_2,CO is appreciably volatile. Further reaction, leading to the formation of the carbonyl, occurs through the vapour at the copper or silver walls of the autoclave. Admixture of finely-divided metals with the cobalt halide greatly increases the yield of carbonyl, the effect increasing in the order $Au < Pt < Ag < Cu < Cd$ or Zn. A. A. Blanchard and P. Gilmont [24] have studied the preparation of cobalt carbonyl, nitrosylcarbonyl, and carbonyl hydride by the cyanide method. Carbon monoxide was found to be absorbed almost quantitatively by an alkaline suspension of a cobalt salt, forming $KCo(CO)_4$, though this reaction took place only when a small amount of cyanide was present. Nitric oxide displaced the volatile cobalt nitrosylcarbonyl, $Co(NO)(CO)_3$, from the resulting solution even when it was distinctly alkaline, whereas acids displaced the volatile cobalt carbonyl hydride $HCo(CO)_4$. The

[21] W. Klemm and W. Tilk, *Z. anorg. Chem.*, 1932, **207**, 175.

[22] *Ibid.*, 1939, **243**, 164.

[23] *Ibid.*, p. 145.

[24] *J. Amer. Chem. Soc.*, 1940, **62**, 1192.

tetracarbonyl $[Co(CO)_4]_2$ was obtained by allowing the hydride to decompose spontaneously at room temperature.

Reduction of tungsten hexachloride and molybdenum pentachloride at $-10°$ to $0°$ by means of carbon monoxide and iron or zinc dust in a mixture of ether and benzene yields the hexacarbonyls, $W(CO)_6$ and $Mo(CO)_6$.[25] Increased initial pressures of the monoxide improve the yields of the carbonyls, which are otherwise of the order of 10—14%; $W(CO)_6$ may also be prepared from $WOCl_4$ in ether by the above method.

Hitherto the existence of complexes of germanium other than the hexafluorogermanates has been doubtful, but evidence has now been put forward[26] which shows chlorogermanic acid and the hexachlorogermanates to be capable of existence. When germanium tetrachloride was dissolved in concentrated hydrochloric acid, migration experiments showed the movement of germanium to the anode, presumably in the form of $GeCl_6''$ ions. Cæsium hexachlorogermanate, Cs_2GeCl_6, has also been prepared by the addition of germanium tetrachloride to a solution of cæsium chloride in 1 vol. of ethyl alcohol and 2 vols. of 12N-hydrochloric acid; it was insoluble in 12N-hydrochloric acid, but dissolved readily in water and was rapidly hydrolysed. It was stable in dry air at room temperature, but was decomposed above 160° without melting. The crystals had a face-centred cubic lattice, with a Ge–Cl distance of 2·35 A.

The existence of a tribromide of nitrogen has not been reported until recently, although the compounds NH_2Br[27] and $NHBr_2$[28] have been prepared. M. Schmeisser[29] has now obtained an ammine of nitrogen tribromide, $NBr_3,6NH_3$, by mixing bromine vapour with excess of ammonia at 1—2 mm. total pressure at 20°. Ammonium bromide is deposited and the new compound condenses as a purplered solid in a trap cooled to $-95°$. It decomposes explosively above $-70°$, according to the equation $NBr_3,6NH_3 = N_2 + 3NH_4Br + 2NH_3$. This reaction establishes the constitution, for no other substances likely to be formed under the conditions given (e.g., an ammine of bromine) would yield these decomposition products in the observed ratio.

[25] K. A. Kotscheschkov, A. N. Nesmejanov, M. M. Nadj, I. M. Rossinskaja, and L. M. Borisova, *Compt. rend. Acad. Sci. U.R.S.S.*, 1940, **26**, 54; K. N. Anisimov and A. N. Nesmejanov, *ibid.*, p. 58.

[26] A. W. Laubengayer, O. B. Billings, and A. E. Newkirk, *J. Amer. Chem. Soc.*, 1940, **62**, 546.

[27] W. Moldenhauer and M. Burger, *Ber.*, 1929, **62**, 1615.

[28] G. H. Coleman, C. B. Yager, and H. Soroos, *J. Amer. Chem. Soc.*, 1934, **56**, 965.

[29] *Naturwiss.*, 1940, **28**, 63.

Metallic phosphides have been the subject of three recent papers. J. L. Andrieux and M. Chêne [30] have prepared MoP and a new subphosphide, Mo_3P, by the electrolysis of a fused mixture of sodium metaphosphate, sodium chloride, and molybdenum trioxide at 800° between carbon electrodes.   Both phosphides resist attack by hydrochloric acid, but are decomposed by sulphuric or nitric acid, fused alkalis, or oxidising agents.   M. Heimbrecht and W. Biltz [31] have not obtained any evidence for the existence of FeP_3, but have prepared an unstable greyish-black phosphide $FeP_{2.57}$ by treatment of a tin–iron alloy (5% of iron) with phosphorus under pressure.   This gives an X-ray diagram distinct from that of FeP_2.   The system iridium–phosphorus has also been studied; [32] the only compounds formed are IrP_2 and Ir_2P.

R. Höltje and H. Schlegel [33] have shown that the action of phosphine on cuprous, argentous, and aurous halides affords the compounds $CuCl,2PH_3$, $CuBr,2PH_3$, CuI,PH_3, AgI,PH_3, and AuI,PH_3 in addition to the known compounds $CuCl,PH_3$, $CuBr,PH_3$, $CuI,2PH_3$, and $2AgI,PH_3$.

Continuing their studies on the constitution of complex metallic salts, F. G. Mann and his co-workers [34] have prepared and examined a wide range of compounds of *tert.*-alkyl-phosphines and -arsines with cadmium and mercuric halides.   The simplest of the cadmium complexes, $[(R_3P)_2CdX_2]$ (class 1), almost certainly has a tetrahedral structure.   Two further types of cadmium compound,

$$[(R_3P)_2(CdX_2)_2]$$
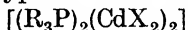
and $[(R_3P)_3(CdX_2)_2]$ (classes 2 and 3), have been obtained; class 2 has the bridged structure typified by (I), and the new type of structure, indicated without differentiation of the planes of the bonds in (II), has been tentatively assigned to class 3.

(I.)   (II.)
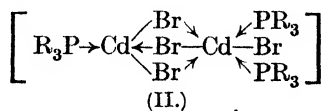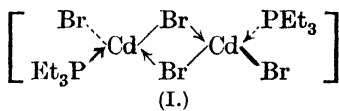
The mercuric halides form five classes of compounds, three of which (classes A, B, and E) are entirely analogous to the cadmium complexes.   Class C, $[(R_3P)_2(HgX_2)_3]$, includes salts with two different types of structure; some members of the series, *e.g.*,

$$[(Pr^a_3As)_2(HgCl_2)_3]$$
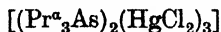
and $[(Bu^a_3As)_2(HgBr_2)_3]$, are shown by X-ray analysis to be molecular compounds of class B complexes with the mercuric halide.   The

[30] *Compt. rend.*, 1939, **209**, 672.   [31] *Z. anorg. Chem.*, 1939, **242**, 233.
[32] K. H. Söffge, M. Heimbrecht, and W. Biltz, *ibid.*, 1939, **243**, 297.
[33] *Ibid.*, p. 246.
[34] R. C. Evans, F. G. Mann, H. S. Peiser, and D. Purdie, *J.*, 1940, 1209.

molecules of the compound $[(Et_3As)_2(HgI_2)_3]$, however, do not possess a centre of symmetry; their structure is possibly (III).

$$\left[\begin{array}{c} \text{I} \diagdown \text{I} \text{I} \diagdown \text{AsEt}_3 \\ \text{Hg}\diagup\diagdown\text{Hg}\diagup\diagdown\text{Hg}\diagup \\ \text{Et}_3\text{As} \diagup \text{I} \text{I} \diagup \text{I} \end{array} \right]$$

(III.)
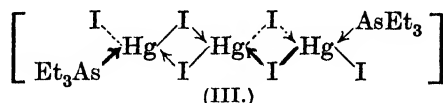
Similar alternative structures (a molecular compound of a class B complex with 2 mols. of mercuric halide, or a structure of type III with an additional ring) appear possible for class D, $[(R_3P)_2(HgX_2)_4]$, but a preliminary X-ray examination indicates that the latter alternative is unlikely, at least for the compounds $[(Et_3P)_2(HgBr_2)_4]$ and $[(Et_3As)_2(HgCl_2)_4]$. In all of the above classes both phosphine and arsine derivatives have been obtained.

Bridged complexes containing both cadmium and mercury have also been prepared.[35] The compound $[(Pr^a_3P)_2CdHgI_4]$, for example, may be obtained (a) from $[(Pr^a_3P)_2CdI_2]$ and mercuric iodide or (b) by boiling an alcoholic solution containing equivalent amounts of $[(Pr^a_3P)_2(CdI_2)_2]$ and $[(Pr^a_3P)_2(HgI_2)_2]$. The second method of preparation indicates that the parent cadmium and mercury compounds of classes 2 and B, to which the product is probably analogous in structure, are partly dissociated in hot alcoholic solution to give the free radicals (IV) and (V). When the

$$(\text{IV.}) \quad \begin{array}{c} Pr^a_3P \diagdown I \\ \text{Cd}\diagup \\ I \diagup \end{array} \qquad\qquad \begin{array}{c} Pr^a_3P \diagdown I \\ \text{Hg}\diagup \\ I \diagup \end{array} \quad (\text{V.})$$

solution cools, these radicals unite in pairs to give the cadmium–mercury complex, which is less soluble than either of the parent compounds. Bridged cadmium–mercury complexes containing mixed halogens, e.g., $[(Pr^a_3P)_2CdHgBr_2I_2]$, or mixed arsine and phosphine groups, e.g., $[(Pr^a_3P)(Pr^a_3As)CdHgI_4]$, are also described. An interesting type of " mixed " bridged complex,

$$[(Pr^a_3As)_2PdHgBr_4],$$
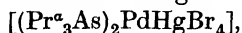
has also been prepared; its molecule is dissymmetrical and contains metal atoms with both planar (Pd) and tetrahedral (Hg) valency distribution (VI). This type is similar to the copper complexes

$$\left[\begin{array}{c} Pr^a_3As \diagdown Br AsPr^a_3 \\ \text{Pd}\diagup\diagdown\text{Hg}\diagup \\ Br \diagup Br Br \end{array} \right] \quad (\text{VI.})$$
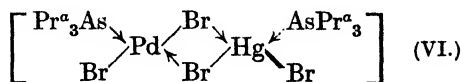
obtained by D. P. Meller, G. J. Burrows, and B. S. Morris.[36]   No analogous palladium–cadmium complexes were formed, and

[35] F. G. Mann and D. Purdie, J., 1940, 1230.
[36] Nature, 1938, 141, 414.

attempts to prepare mixed cuprous– or argentous–mercuric complexes, containing two tetrahedral units, were also unsuccessful.

A chemical proof of the linear configuration of the complexes $[Et_3P \rightarrow AuX]$ and $[Et_3As \rightarrow AuX]$ $(X = Cl, I)$, which is supported by X-ray analysis,[37] has been attempted.[38] These compounds, together with the corresponding bromide, combine readily with a further molecule of halogen to give 4-covalent auric complexes of the type $[Et_3P \rightarrow AuX_3]$, which should have a planar structure. If the two halogen atoms enter the vacant *trans*-positions of the linear 2-covalent complex, two isomerides of a compound such as $[Et_3P \rightarrow AuBrI_2]$ should be formed by (a) addition of iodine to $[Et_3P \rightarrow AuBr]$, and (b) addition of iodine monobromide to $[Et_3P \rightarrow AuI]$. In the several cases tried the two methods of preparation gave identical products. It was concluded that the co-ordinated groups in the auric compound are mobile and therefore adopt positions giving maximum stability, as in the case of certain 4-covalent palladous complexes.

The chemistry of the oxides of niobium has been clarified by recent work. According to G. Grube, O. Kubaschewski, and K. Zwiauer,[39] the oxides NbO_2, NbO, and Nb_2O may be obtained by reduction of the pentoxide with a mixture of hydrogen and water vapour under appropriate conditions; NbO_2 is also obtained by heating the pentoxide in argon at 1150—1300°. The individuality of all these oxides is proved by Debye–Scherrer photographs, but the supposed oxide Nb_2O_3 is shown to be a mixture of NbO and NbO_2. Although the claim to have reduced Nb_2O_5 to Nb_2O with hydrogen has been contested by G. Brauer,[40] this reaction has since been confirmed.[41] Brauer finds that the pentoxide exists in at least two forms, one of which is obtained when niobic acid, precipitated from aqueous solution, is dehydrated at 600—800°. When this form is heated above 800° a modification of the oxide giving a different X-ray pattern results. The m. p. of niobium pentoxide in an atmosphere of oxygen is 1460°. NbO_2 was prepared by Brauer by heating Nb_2O_5 with niobium or hydrogen, and this oxide, when heated with the metal at 1750° in argon, gave NbO. Intermediate phases of the type NbO_x $(x = 2\cdot0—2\cdot5)$ were prepared by heating mixtures of Nb_2O_5 and NbO_2 at 1400°. P. Süe[42] has studied the equilibrium $Nb_2O_5 + C \rightleftharpoons Nb_2O_4 + CO$ at 715—840°, and has found the heat of formation of Nb_2O_4 to be 393 kg.-cals.

[37] F. G. Mann, A. F. Wells, and D. Purdie, *J.*, 1937, 1828.

[38] *J.*, 1940, 1235.   [39] *Z. Elektrochem.*, 1939, **45**, 885.

[40] *Naturwiss.*, 1940, **28**, 30.

[41] O. Kubaschewski, *Z. Elektrochem.*, 1940, **46**, 284.

[42] *J. Chim. physique*, 1939, **36**, 280.

The hydrolysis of sulphur mono- and di-chlorides, known previously to be a reaction of considerable complexity, has recently been studied in some detail. According to G. Holst,[43] treatment of either chloride with potassium hydroxide in 95% ethyl-alcoholic solution results in immediate neutralisation of 2 mols. of the alkali, of which a further 2 mols. are neutralised in a subsequent slow reaction. The initial rapid reaction is ascribed to the formation of $S_2(OH)_2$ and $S(OH)_2$, from the mono- and di-chloride, respectively, and the slower change, which is almost inhibited in 99·5% alcohol, to the further hydrolysis of these compounds. B. S. Rao,[44] confining his attention to the monochloride, has studied the hydrolysis products in greater detail. The reaction occurs rapidly and completely at the interface between a solution of sulphur monochloride in carbon tetrachloride and aqueous sodium hydroxide, to which cadmium chloride is added to react with any sulphide formed. The products are free sulphur, sulphide, sulphite, and thiosulphate, with sulphate and trithionate if dilute alkali is used. All these substances can be formed by secondary reactions of S_2O or $S_2(OH)_2$ which, in accordance with Holst's conclusion, is regarded as the primary hydrolysis product. The compound $S_2(OH)_2$ may correspond in constitution with the hypothetical thiosulphurous acid. The existence of disulphur monoxide, S_2O, has been confirmed by Rao,[45] who prepared it by passing sulphur monoxide into dry carbon tetrachloride at $-12°$ to $-18°$. The reactions of the resulting deep yellow liquid were thought to indicate the presence of S_2O, formed by the reactions $2SO = S_2O_2$; $SO + S_2O_2 = S_2O + SO_2$. The S_2O decomposes on keeping according to the equation $2S_2O = 3S + SO_2$. Cryoscopic measurements show that the carbon tetrachloride solutions actually contain S_2O in the form of a complex with dissolved sulphur, to which the formula S_8,xS_2O ($x = 3$ or 4) is assigned. The hydrolysis products of these solutions correspond with those of similar solutions of S_2Cl_2.

The preparation and properties of sulphur monoiodide and thionyl iodide have been examined by M. R. A. Rao.[46] Both are obtained by treating a carbon tetrachloride solution of the corresponding chloride with dry potassium iodide; the resulting solutions in carbon tetrachloride are unstable at room temperature and their decomposition is promoted by light. The hydrolysis products of the monoiodide are analogous to those obtained with sulphur monoiodide, but thionyl iodide and alkali give sulphur, sulphite, thiosulphate, iodide, and hypoiodite, the latter resulting from

[43] *Bull. Soc. chim.*, 1940, [v], **7**, 276.
[44] *Proc. Indian Acad. Sci.*, 1939, **10**, *A*, 423.
[45] *Ibid.*, p. 491.   [46] *Ibid.*, 1940, **11**, *A*, 162, 185.

iodine formed in the primary reaction. The amount of thio-sulphate formed is greater than that produced in the hydrolysis of thionyl bromide. The decomposition of sulphur monoiodide and thionyl iodide and their absorption spectra have been studied in some detail.[47]

The existence of a selenium iodide, Se_nI_2 (n undetermined), is indicated by the absorption spectrum of mixtures of selenium and iodine dissolved in carbon disulphide, and by a study of the equi-librium between the two elements in carbon tetrachloride solution.[48] The pure hydroselenides of sodium, potassium, rubidium, and caesium have been prepared by W. Teichert and W. Klemm [49] by the action of hydrogen selenide on the ethoxides in anhydrous alcohol, with exclusion of moisture and oxygen. The crystal structure of these compounds has been studied, and they have been shown to resemble the hydrosulphides. The sodium, potassium, and rubidium compounds have a rhombohedrally distorted sodium chloride structure at room temperature, and the sodium chloride structure at higher temperatures, whereas the caesium compound has the caesium chloride structure. The radii of the SH' and SeH' ions are 1·98 and 2·11 A., respectively.

Recent studies on affinity by W. Biltz and his collaborators have included the system uranium–sulphur,[50] in which the compounds US_2, U_2S_3, US_3, and U_4S_3 are formed, the last two being new; US_3 is prepared by the action of S on US_2 at 600—800°, excess sulphur being removed either by volatilisation in a vacuum at 300° or by extraction with carbon disulphide. The formula of the sub-sulphide U_4S_3 has been confirmed by X-ray analysis.[51] A new oxide of uranium, U_2O_5, has been obtained by R. Lydén [52] by prolonged treatment of U_3O_8 with potassium hydrogen carbonate solution at 100°. The reaction is represented by the equation $U_3O_8 + 4KHCO_3 = K_4[UO_2(CO_3)_3] + U_2O_5 + CO_2 + 2H_2O$, and appears to support the formula UO_3,U_2O_5 for U_3O_8. This formula is also indicated by measurements of the magnetic susceptibility.[53]

A simple method has been described for conversion of platinum, iridium, rhodium, and palladium into their double caesium chlorides.[54] The metal is mixed with caesium chloride and treated with ammon-ium chloride vapour and oxygen at a red heat; attack is due to

[47] M. R. A. Rao, *Proc. Indian Acad. Sci.*, 1940, **11**, *A*, 175, 201.

[48] J. D. McCullough, *J. Amer. Chem. Soc.*, 1939, **61**, 3401.

[49] *Z. anorg. Chem.*, 1939, **243**, 86.

[50] E. F. Strotzer, O. Schneider, and W. Biltz, *ibid.*, 1940, **243**, 307.

[51] M. Zumbusch, *ibid.*, p. 322.

[52] *Finska Kem. Medd.*, 1939, **48**, 124.

[53] H. Haraldsen and R. Bakken, *Naturwiss.*, 1940, **28**, 127.

[54] M. Delépine, *Bull. Soc. chim.*, 1939, [v], **6**, 1471.

chlorine formed from hydrogen chloride and oxygen. Electrolytic reduction of solutions of ruthenium trichloride in hydrochloric acid gives solutions containing Ru·· or Ru·, or metallic Ru, according to the conditions; [55] Ru·· is moderately stable in 2N-hydrochloric acid, but Ru· readily gives Ru·· and Ru. J. Meyer and H. Kienitz [56] have described the preparation of $RhF_3,6H_2O$, M_3RhF_6 (M = K, Rb, Cs), $RhBr_3,2H_2O$, and RhI_3, together with numerous new diazido- and triazido-complex salts, and have also studied the constitution of solutions of rhodium trichloride in various solvents.

Renewed interest in polyiodides and related compounds is shown by the appearance during the year of papers dealing with ammonium, sodium, potassium, and rubidium polyiodides. In each case the compounds formed were identified by a systematic study of the ternary system alkali iodide–iodine–solvent, the customary wet-residue method being used. In a particularly thorough isothermal and polythermal study of the ammonium compounds,[57] with water as solvent, the existence of the solid phases NH_4I_3, $NH_4I_3,3H_2O$, and possibly NH_4I_5,H_2O has been established; NH_4I_3 also appears as a solid phase in the binary system ammonium iodide–iodine.[58] The known polyiodides of rubidium and cæsium occur only in the anhydrous state or as organic solvates, whereas those of lithium, sodium, and potassium appear to exist mainly in hydrated forms : ammonium, giving both types, provides a transition between these two classes. The sodium iodide–iodine–water system [59] is unusual in that the polyiodide phases which exist at 0°, viz., $NaI_4,2H_2O$ and (probably) $NaI_2,3H_2O$, apparently contain an even number of iodine atoms combined with each sodium atom ; the preparation of a few other even polyhalides (e.g., $CsBr_4$, CsI_4) has been claimed, but the sodium di-iodide is unique. It is suggested that the even polyhalides may be molecular compounds, the components of which contain odd numbers of halogen atoms, e.g., $NaI,NaI_3,6H_2O$ or $NaI_3,NaI_5,4H_2O$. A study of the potassium polyiodides,[60] conducted on similar lines to that of the ammonium compounds, shows that the solid phases KI_3,H_2O, KI_7,H_2O, and two polymorphic forms of $KI_3,2H_2O$ occur in aqueous systems ; the first two compounds had been obtained previously by N. S. Grace.[61] With

[55] G. Grube and H. Nann, *Z. Elektrochem.*, 1939, **45**, 874.

[56] *Z. anorg. Chem.*, 1939, **242**, 281.

[57] T. R. Briggs, K. H. Ballard, (Miss) F. R. Alrich, and J. P. Wikswo, *ibid.*, p. 325.

[58] T. R. Briggs, and K. H. Ballard, *J. Physical Chem.*, 1940, **44**, 322.

[59] G. H. Cheesman, D. R. Duncan, and I. W. H. Harris, *J.*, 1940, 837.

[60] T. R. Briggs, K. D. G. Clack, K. H. Ballard, and W. A. Sassaman, *J. Physical Chem.*, 1940, **44**, 350.

[61] *J.*, 1931, 594.

toluene as solvent the only rubidium polyiodide stable in the solid state at 6° or 25° is RbI_3, but with benzene the solvated compounds $RbI_7,4C_6H_6$ and $RbI_8,4C_6H_6$ can be obtained at either of these temperatures.[62]   A polyhalide $KI_6CNS,4C_6H_6$, which is analogous to $RbI_7,4C_6H_6$ and contains the thiocyanate radical as a pseudo-halogen, has also been obtained in the system potassium thio-cyanate–iodine–benzene at 6°.   Attempts to prepare compounds of iodine with sodium bromide, potassium bromide, ammonium bromide, thallous bromide, sodium thiocyanate, or ammonium thiocyanate, with benzene or toluene as solvent at 6°, were un-successful, but cæsium bromide gave the known compound $CsBrI_2$.[63] Attempts have also been made [64] to prepare the higher iodides of copper, iron, silver, and thallium by treating metallic copper or iron, silver iodide, or thallous iodide with iodine and benzene or toluene at 6°; in the first three cases FeI_2, CuI, and AgI were the only iodides which resulted, but thallium gave the compounds Tl_6I_8 and TlI_3.

There has been sustained interest in reactions in non-aqueous solutions.   It has been found, for example,[65] that, in presence of certain metallic oxide catalysts, potassamide reacts slowly with potassium nitrate and yields the nitrite : $3KNH_2 + 3KNO_3 \longrightarrow 3KOH + N_2 + NH_3 + 3KNO_2$.   The best catalysts are ferric oxide, cobaltic oxide, and nickelous oxide, although cupric oxide and Mn_3O_4 are moderately active.   In all instances the catalyst is slowly attacked by the potassamide and a potassium ammono-metallate, e.g., $CuNK_2,xNH_3$ is formed.   Reaction between potas-sium nitrite and potassamide in liquid ammonia is very slow, although at higher temperatures and in absence of a catalyst the following reaction occurs : $KNO_2 + KNH_2 \longrightarrow 2KOH + N_2$.

The action of liquid ammonia on the sulphur trioxide addition compounds with pyridine, dimethylaniline, dioxan, hydrogen chloride, and sodium chloride results in ammonolysis, the chief product being ammonium sulphamate, $NH_2 \cdot SO_3NH_4$.[66]   Ammon-ium imidodisulphonate is also formed, its amount increasing as the stability of the sulphur trioxide addition compound diminishes. In this connexion, the same authors have also studied the production of sulphamic acid in the reaction between hydroxylamine sulphate and sulphur dioxide.[67]

W. Klatt [68] has found that, although hydrazoic acid and hydrogen

[62] H. W. Foote and M. Fleischer, *J. Physical Chem.*, 1940, **44**, 633.
[63] *Idem, ibid.*, p. 640.   [64] *Idem, ibid.*, p. 647.
[65] F. W. Bergstrom, *J. Amer. Chem. Soc.*, 1940, **62**, 2381.
[66] H. H. Sisler and L. F. Audrieth, *ibid.*, 1939, **61**, 3392.
[67] *Ibid.*, p. 3389.   [68] *Z. physikal. Chem.*, 1939, **185**, 306.

cyanide are almost insoluble in anhydrous hydrofluoric acid and most azides and cyanides are decomposed, silver and mercuric azides and mercuric cyanide dissolve and can be recovered unchanged. From the boiling-point elevations produced, it is deduced that ionisation takes place into F' and cations such as $(AgN_3H)^{\cdot}$ and $[Hg(CN)_2H]^{\cdot}$.

Further support for the view that pyridine and compounds of the same type function as bases in selenium oxychloride solution is afforded by the isolation of addition compounds of pyridine, quinoline, and *iso*quinoline with selenium oxychloride.[69]   With pyridine there are two such compounds, $C_5H_5N,SeOCl_2$ and $(C_5H_5N)_2SeOCl_2$, ionisation of the first yielding $(C_5H_5NSeOCl)'$ and Cl'.

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2. THE BORON HYDRIDES.

The classical investigations of A. Stock and his collaborators on the boron hydrides added enormously to our knowledge of this important group of compounds.   Indeed, it appeared at one time that little remained to be completed.   During the last ten years, however, there has been a marked revival of interest in these compounds, both from the point of view of preparative chemistry and in so far as problems of valency and molecular structure are concerned.   Stock's contributions to this subject have been adequately summarised elsewhere,[1] but it would seem useful to review in some detail the more recent developments.

The method used by Stock in preparing boron hydrides was the decomposition of magnesium boride, obtained by heating together a mixture of magnesium and boric oxide, with either 10% hydrochloric acid or, better, as E. Wiberg and K. Schuster [2] subsequently found, 8N-phosphoric acid.   The use of phosphoric acid increases the yield under the best conditions from about 4 to about 11%.   The volatile products obtained are the hydride B_4H_{10}, mixed with small amounts of B_5H_9, B_6H_{10}, $B_{10}H_{14}$, carbon dioxide, hydrogen sulphide, silicon hydrides, and phosphine, and the separate hydrides are obtained from this complex mixture by a laborious process of fractional distillation and condensation in an all-glass vacuum apparatus.   Diborane, B_2H_6, which may be regarded as the chief hydride, is not formed directly in the reaction, but is obtained

[69] J. Jackson and G. B. L. Smith, *J. Amer. Chem. Soc.*, 1940, **62**, 544.

[1] See A. Stock, "Hydrides of Boron and Silicon," Cornell University Press, 1933.

[2] *Ber.*, 1934, **67**, 1805.

together with B_5H_9, $B_{10}H_{14}$, and possibly also a further hydride of the formula B_6H_{12}, by heating tetraborane, B_4H_{10}, at $100°$.

For reference purposes, the formulæ, physical properties and stability of these hydrides are tabulated below :

	B_2H_6.	B_4H_{10}.	B_5H_9.	B_5H_{11}.	B_6H_{10}.	$B_{10}H_{14}$.
B. p.	$-92.5°$	$18°$	—	—	—	$ca.\ 213°$
V. p. at $0°$, mm. ...	—	388	66	53.0	7.2	—
M. p.	$-165.5°$	$-120°$	$-46.6°$	$-123.3°$	$-65.1°$	$99.6°$
Decomp. by H_2O...	Very rapid	Slow	Slow	—	Slow	Very slow
Stability	High	Low	High	Very low	Low	Very high

In 1931, A. B. Burg and H. I. Schlesinger [3] developed an entirely new and considerably more efficient method for preparing the simplest of these hydrides, diborane. A mixture of boron trichloride vapour and hydrogen was passed at a high streaming rate and at a pressure of 5—10 mm. through an electrical discharge formed between water-cooled copper electrodes. The products escaping from the discharge zone consisted of much unchanged boron halide, mixed with hydrogen, hydrogen chloride, monochlorodiborane, B_2H_5Cl, and a small amount of diborane. In addition, a resinous yellow-brown solid was deposited near the discharge. This evolved hydrogen when treated with alkali and contained ill-defined, solid boron hydrides of the type described by Stock, which are formed in all experiments involving pyrolysis at moderate temperatures. The isolation of the comparatively non-volatile mixture of boron trichloride and monochlorodiborane is easy, and when kept at $0°$ the second of these compounds disproportionates according to the equation : $6B_2H_5Cl = 5B_2H_6 + 2BCl_3$. The resulting diborane is again easy to isolate owing to its high volatility.

Burg and Schlesinger noted that boron tribromide undergoes a similar reaction with hydrogen in the discharge, but the advantages of using the bromide in place of the chloride were first emphasised by A. Stock and W. Sütterlin,[4] who found that it was difficult to free diborane from hydrogen chloride and recommended the use of metallic potassium for this purpose. Boron tribromide, on the other hand, is more easily manipulated than the trichloride, owing to lower volatility, and hydrogen bromide and diborane are also separated with ease. Either of these halides gives a much better yield of hydride than is obtained from magnesium boride; indeed, it may be as high as 80% of the halide reacting,[5] and there is no

[3] J. Amer. Chem. Soc., 1931, 53, 4321.

[4] Ber., 1934, 67, 407; see also A. Stock, H. Martini, and W. Sütterlin, Ber., 1934, 67, 396.

[5] A. Stock and W. Sütterlin, ibid., p. 410.

doubt that this new preparative method has been an important factor governing the success of recent studies in this field.

Burg and Schlesinger's method yields only diborane, and it is important to determine how this may be converted into the other hydrides. Progress in this direction was reported in 1933,[6] when it was shown that other hydrides were formed by heating diborane to moderate temperatures. A flow method was developed, diborane being passed at 14—30 c.c./min. through a glass U-tube held at 100—120°. The two hydrides B_4H_{10} and B_5H_{11} are produced and may be isolated. The thermal decomposition of B_5H_{11} was investigated next, and at 100° it was found to yield H_2, B_2H_6, B_4H_{10}, B_5H_9, $B_{10}H_{14}$, and a non-volatile yellow solid. The yields of B_5H_9 and $B_{10}H_{14}$ increased with the period of heating, but addition of a large excess of hydrogen to B_5H_{11} retarded the formation of the less volatile products and made it possible to obtain reasonable yields of B_4H_{10} and B_2H_6. The importance of these observations lies in the fact that, owing to the complex equilibrium between the various hydrides of boron, any member of the series may be synthesised, while at the same time the improved method for preparing diborane is utilised.

Burg and Schlesinger's subsequent studies in this field have centred round the problem of the structure of the hydrides and have dealt particularly with the investigation of factors which affect the stability of the boron–boron bond. An early investigation of this sort resulted in the preparation of dimethoxyborine, $BH(OMe)_2$, by the interaction of diborane and methyl alcohol.[7] These substances react readily at room temperature with evolution of hydrogen. The product, which boils at 25·9° and is not associated in the gas phase, is rapidly hydrolysed, $BH(OMe)_2 + 3H_2O = B(OH)_3 + 2MeOH + H_2$, and also decomposes reversibly according to the equation $6BH(OMe)_2 \rightleftharpoons B_2H_6 + 4B(OMe)_3$. No volatile monomethoxyborine was formed in the reaction with alcohol, but a white non-volatile solid was obtained which was thought to be a polymer of this substance. Other alkoxyborines were isolated in a subsequent investigation of the reaction of diborane with organic compounds containing a carbonyl group,[8] and are referred to later.

Methyl-substituted derivatives of diborane are formed in the reaction between diborane and trimethylboron at room temperature.[9] By varying the proportion of the alkylboron, four derivatives, B_2H_5Me, $B_2H_4Me_2$, $B_2H_3Me_3$, and $B_2H_2Me_4$, are obtainable, but

[6] A. B. Burg and H. I. Schlesinger, *J. Amer. Chem. Soc.*, 1933, **55**, 4009.

[7] *Idem, ibid.*, p. 4020.

[8] H. C. Brown, H. I. Schlesinger, and A. B. Burg, *ibid.*, 1939, **61**, 673.

[9] H. I. Schlesinger and A. O. Walker, *ibid.*, 1935, **57**, 621.

even with a large excess of the alkyl there is no indication of the formation of either the penta- or the hexa-methyl derivative.

The structure of the methylboranes was determined by vapour-density measurements, hydrolysis, and oxidation. On treatment with water at room temperature they break down at the boron–boron bond, yielding 2 mols. of boric or methylboric acids, *e.g.*

$$BHMe_2 \cdot BH_2Me \longrightarrow B(OH)Me_2 + B(OH)_2Me$$
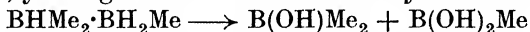
The unsymmetrical dimethyl compound tends always to be formed in greater quantity than its homologues. For instance, with equal volumes of the two reagents a mixture was obtained consisting of $8 \cdot 1\%$ of mono-, $81 \cdot 6\%$ of unsymmetrical di-, $8 \cdot 0\%$ of tri-, and $2 \cdot 3\%$ of tetra-methyldiborane. In the trimethyl derivative two of the methyl groups are attached to one boron atom and one to the other, while the tetramethyl derivative yields 2 mols. of dimethylboric acid on hydrolysis and is therefore symmetrical.

Monomethyldiborane is the least stable of these substances and has a marked tendency to revert to diborane and trimethylboron. This accords with the observation, already noted, that monochloro-diborane disproportionates to form diborane and boron trichloride. These observations as a whole also support Stock's conclusion that the boron–boron bond can exist only so long as each boron atom is attached to one hydrogen atom.

The symmetrical dimethyl derivative of diborane, which is not formed in the above reaction, is prepared by treating the mono-methyl derivative with dimethyl ether at $-80°$.[10] Fission of the boron–boron bond occurs, and the borine radical, BH_3, forms a co-ordination compound, $Me_2O \rightarrow BH_3$, with the ether. The liberated BH_2Me radicals, which are unable to form a similar compound, combine to produce $(BH_2Me)_2$, the symmetrical dimethyldiborane.

Other alkyl derivatives of diborane are entirely analogous to the methyl derivatives. The four ethylboranes and mono- and di-*n*-propyldiborane are obtained by the reactions of triethylboron and tri-*n*-propylboron, respectively, with the parent hydride.[11] There was evidence of the formation of further-substituted propyl derivatives, but the lack of volatility, a serious handicap in work of this type which utilises in the main the special technique developed by Stock, prevented their isolation.

Direct evidence for the transitory existence of the borine radical, BH_3, is afforded by the formation of the compound borine carbonyl, BH_3CO, by the interaction of diborane and carbon monoxide.[12]

[10] H. I. Schlesinger, N. W. Flodin, and A. B. Burg, *J. Amer. Chem. Soc.*, 1939, **61**, 1078.

[11] H. I. Schlesinger, L. Horvitz, and A. B. Burg, *ibid.*, 1936, **58**, 407.

[12] A. B. Burg and H. I. Schlesinger, *ibid.*, 1937, **59**, 780.

When these two substances are heated together an equilibrium is set up ($B_2H_6 + 2CO \rightleftharpoons 2BH_3CO$), the position of which is such that a sample of borine carbonyl at 200 mm. pressure would be 95% decomposed at 100°. The time for equilibrium to be established is of the order of 15 mins. at 100°, but at room temperature reaction is very slow. As a result it is possible by rapid cooling of a mixture in equilibrium at 100° to isolate borine carbonyl, which has b. p. $-64°$, and has been proved by vapour-density determinations to have the monomeric formula. The compound is formulated with a co-ordinate bond between the carbon and the boron atom.

Borine carbonyl is decomposed by heating with water at 100° [$BH_3CO + 3H_2O = B(OH)_3 + 3H_2 + CO$]. With gaseous ammonia it forms an addition compound $BH_3(CO)(NH_3)_2$, a fairly stable white solid which reacts with a solution of sodium in liquid ammonia, evolving hydrogen. From the quantity of hydrogen, it is concluded that the compound contains two ammonium ions per molecule of borine carbonyl, but its exact nature is not yet known.

It was as a result of the study of this reaction with ammonia, which had been expected to displace carbon monoxide from the borine carbonyl, that the interaction of borine carbonyl and trimethylamine was subsequently studied. This amine was found to displace carbon monoxide rapidly and completely at room temperature according to the equation :

$$BH_3CO + NMe_3 = Me_3N,BH_3 + CO$$
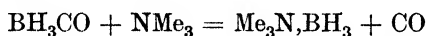
The reaction takes place only at temperatures which are sufficiently high to cause dissociation of the carbonyl itself. Thus, although there is no observable displacement of carbon monoxide at $-80°$, reaction is rapid at 20°. As would be anticipated from this result, diborane also reacts readily with trimethylamine to give the same product, Me_3N,BH_3, which is a solid of m. p. 94—94·5° and (extrapolated) b. p. 171°.

The reaction of diborane with ammonia to form the diammoniate, $B_2H_6,2NH_3$ [13] and the decomposition of this when heated in a sealed tube, with formation of the volatile cyclic compound $B_3N_3H_6$, are already well known. The analogous reactions of the methylboranes were investigated by H. I. Schlesinger, L. Horvitz, and A. B. Burg.[14] The ammonia derivatives were prepared by condensing the methylborane under examination with an excess of ammonia, holding the mixture at $-115°$ for 15 mins., and then raising the temperature gradually to $-78·5°$, at which point the unreacted ammonia was pumped off. Loss of ammonia ceased in

[13] A. Stock and E. Kuss, *Ber.*, 1923, **56**, 807.
[14] *J. Amer. Chem. Soc.*, 1936, **58**, 409.

each instance when the molecular ratio of combined ammonia to methylated borane was approximately 2 : 1, showing that compounds analogous to the diammoniate of diborane were formed. They were white powders, which were more stable than the methyldiboranes themselves, although less stable than the ammoniate of the unmethylated hydride. The diammoniate of monomethyldiborane may be heated to 50° without change, but above this temperature evolution of hydrogen begins : the corresponding compound of dimethylborane loses hydrogen at 10°, and the others begin to decompose at − 35°.

The ammonia derivatives decompose rapidly at 180—200°, and by these reactions aminodimethylborine, $BMe_2 \cdot NH_2$, and the cyclic compounds $B_3N_3H_6$, $MeB_3N_3H_5$, $Me_2B_3N_3H_4$, and $Me_3B_3N_3H_3$ have been prepared. An alternative method is to heat the methylated hydride directly with ammonia at 180—200°. Aminodimethylborine is one of the chief products of the pyrolytic action of ammonia on di-, tri-, or tetra-methyldiborane. The other compounds are derivatives of $B_3N_3H_6$, in which one or more hydrogen atoms of the BH groups are replaced by methyls. The m. p.'s and b. p.'s of the four ring compounds are tabulated below.

	M. p.	B. p.			M. p.	B. p.
$B_3N_3H_6$	−58°	53°	$B_3N_3H_4Me_2$	...	−48°	107°
$B_3N_3H_5Me$	−59	87	$B_3N_3H_3Me_3$	...	31·5	129

The chief evidence on which these compounds are formulated is a quantitative study of the hydrogen evolution on hydrolysis, it being assumed that free hydrogen results only from hydrolysis of the B–H bonds.

The synthesis of N-methyl derivatives of triborinetriamine, as distinct from the B-methyl derivatives mentioned above, calls for a different method, but has been achieved by heating together mixtures of diborane, ammonia and methylamine.[15] Such mixtures were heated in sealed tubes in an oil-bath at 200° for 15—30 minutes. The product contained hydrogen, triborinetriamine, and its N-methyl derivatives in proportions depending upon the ratio of methylamine to ammonia, and was analysed by fractional condensation of the components of the mixture in the vacuum apparatus. Three methyl derivatives were isolated and fully characterised, their formulæ and b. p.'s being tabulated below together with those of three NB-methyl compounds obtained by the reaction of trimethylboron with mono-N-methyltriborinetriamine. These substitution products are formed simultaneously; the fact that only six deriv-

[15] H. I. Schlesinger, D. M. Ritter, and A. B. Burg, J. Amer. Chem. Soc., 1938, **60**, 1296.

atives exist is to be regarded as confirmation of the cyclic structure of $B_3N_3H_6$.

	B. p.		B. p.
N-Me$B_3N_3H_5$	84°	NB-Me$_2B_3N_3H_4$	124°
N-Me$_2B_3N_3H_4$	108	NBB'-Me$_2B_3N_3H_3$	139
N-Me$_3B_3N_3H_3$	134	$NBB'B''$-Me$_4B_3N_3H_2$	158

The structures of the cyclic compound $B_3N_3H_6$ and of its substitution products have been conclusively settled by electron-diffraction experiments,[16] but they have become far more comprehensible as the result of a further publication by H. I. Schlesinger and A. B. Burg [17] on the structure of the diammoniate of diborane. E. Wiberg [18] considered this compound to be a true salt and assigned to it the formula $(NH_4)_2{}^{++}(H_2B{=}BH_2)^{--}$. On the other hand, 1 g.-mol. of a true diammonium salt when dissolved in liquid ammonia should react with 2 g.-atoms of sodium and liberate 2 g.-equivs. of hydrogen, whereas Burg and Schlesinger found that only 1 equiv. of hydrogen was set free. Only when the reaction temperature was allowed to rise above $-77°$ was further hydrogen evolved as a result of secondary reactions. The ammoniate was accordingly formulated as $NH_4{}^+[BH_3.NH_2.BH_3]^-$, a structure which contains the B–N–B skeleton and provides a clue to the formation of the cyclic molecule $B_3N_3H_6$ by thermal decomposition.

The use of excess of diborane in preparing the diammoniate gives rise to a new volatile compound B_2H_7N (b. p. 76·2°; m. p. $-66·5°$). A detailed study of this substance [19] showed that it was most readily prepared by exposing the diammoniate to diborane at 85—100°, whereby, with a flow method, 19—33% yields of B_2H_7N based on the diborane used were recorded. This compound may be kept for some days at room temperature but decomposes fairly rapidly at 45°. With trimethylamine at $-80°$ it forms a stable addition product Me$_3$N,B_2H_7N, and heating of this with excess of trimethylamine leads to the removal of a BH_3 group with the production of 1 mol. of borine trimethylamine per mol. of B_2H_7N originally used.

Ammonia, like trimethylamine, adds on to B_2H_7N and forms a solid monoammoniate, B_2H_7N,NH_3, which, when rapidly heated to 200°, gives a 45% yield of $B_3N_3H_6$. This is a somewhat greater yield than is obtained by heating the diammoniate of diborane. When B_2H_7N,NH_3 is dissolved in liquid ammonia and treated with sodium, 1 g.-equiv. of hydrogen is liberated per mol. of B_2H_7N used.

[16] A. Stock and R. Wierl, *Z. anorg. Chem.*, 1931, **203,** 228; S. H. Bauer, *J. Amer. Chem. Soc.*, 1938, **60,** 524.

[17] *Ibid.*, p. 290.

[18] *Ber.*, 1936, **69,** 2816.

[19] H. I. Schlesinger, D. M. Ritter, and A. B. Burg, *J. Amer. Chem. Soc.*, 1938, **60,** 2297.

The structures (I) and (II) are thought to represent B_2H_7N and its ammoniate, the NH_3 molecule in (II) being bound by a co-ordinate link to the boron atom.

<pre>
          H H H   H H H H
          .. ..
   (I.)   B : N : B : H   H : N : B : N : B : H   (II.)
          .. ..
          H H H   H H H H
</pre>

The reaction between phosphine and diborane affords an interesting parallel with the ammonia reaction, for 2 vols. of phosphine react at $0°$ to $-20°$ with 1 vol. of diborane, forming the solid compound $B_2H_6,2PH_3$.[20] This is less stable than the diammoniate; it dissociates above $-30°$, the dissociation pressure at $0°$ being 200 mm. The compound separates from the gaseous phase as long, white, needle-shaped crystals which inflame spontaneously in the air, and are decomposed rapidly by water to form hydrogen, phosphine, and boric acid. When it is heated rapidly to $200°$, hydrogen is evolved and a non-volatile residue is obtained which was not identified. It is clearly established, however, that no volatile substance corresponding to $B_3N_3H_6$ is produced.

The compound $B_2H_6,2PH_3$ dissolves slowly in liquid ammonia without apparent reaction. It should be noted that a true phosphonium salt would dissolve with complete evolution of phosphine (e.g., $PH_4Br \xrightarrow{NH_3} PH_3 + NH_4Br$). The solution of $B_2H_6,2PH_3$ in liquid ammonia evolves phosphine slowly at $-60°$, but the amount does not exceed about 55% of the total combined. When the solvent ammonia is pumped away, a solid residue remains which approximates to B_2H_6,PH_3,NH_3, and it is suggested that this should be formulated as $NH_4(BH_3.PH_2.BH_3)$. Gaseous ammonia also displaces 21—57% of the phosphine from the addition compound, the amount depending on the conditions, while hydrogen chloride reacts to form chlorinated derivatives. Under controlled conditions the reaction is

$$B_2H_6,2PH_3 + 2HCl = B_2H_4Cl_2,2PH_3 + 2H_2$$
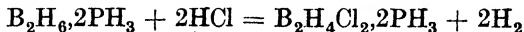
The product is a clear non-volatile liquid, which will react further with hydrogen chloride, forming a white crystalline solid, $B_2H_2Cl_4,2PH_3$. By treatment with hydrogen chloride under pressure this is converted into BCl_3,PH_3, a compound which was originally prepared by J. A. Besson [21] by the interaction of boron trichloride and phosphine below $20°$.

Methyl derivatives of diborane react with trimethylamine in the

[20] E. L. Gamble and P. Gilmont, *J. Amer. Chem. Soc.*, 1940, **62**, 717.
[21] *Compt. rend.*, 1890, **110**, 516.

same way as diborane itself.[22] The fully methylated compound BMe_3,NMe_3 is prepared by treating trimethylboron with a slight excess of trimethylamine, and is a stable solid which melts at 120° and can be sublimed in a vacuum. The vapour is 70% dissociated at 80°. In a similar way trimethylamine reacts with tetramethyl-diborane and with symmetrical dimethylborane, forming the compounds $BHMe_2,NMe_3$ and BH_2Me,NMe_3. In these derivatives the stability (as measured by the dissociation of the vapour) decreases as the number of methyl groups substituted in the borine radical increases. There is also a step-wise gradation in the rates of reaction of these compounds with gaseous hydrogen chloride : only with the trimethyl derivative, BMe_3,NMe_3, is the B–N link broken by this reagent. The equations representing the reaction in the other instances are :

$$BH_3,NMe_3 + HCl \quad = BH_2Cl,NMe_3 + H_2$$
$$BH_2Me,NMe_3 + HCl = BHMeCl,NMe_3 + H_2$$
$$BHMe_2,NMe_3 + HCl = BMe_2Cl,NMe_3 + H_2$$
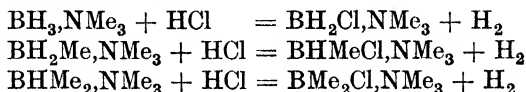
Methylboric acid, which is of interest as being a hydrolysis product of certain methylated boron compounds, has been prepared recently by A. B. Burg,[23] using the reaction between methylmagnesium iodide and methyl borate. This method has been applied in the preparation of other alkylboric acids.[24] The crude acid was de-hydrated by passage over dehydrated calcium sulphate, and the resulting anhydride was found to melt at − 38° and to have an (extrapolated) b. p. of 79°. Pure methylboric acid was formed by the addition of water to the anhydride, and was found to be extensively dissociated in the vapour phase, the b. p. being about 100°.

The anhydride was found to have the trimeric formula $(BMeO)_3$, and in this respect resembled phenylboric anhydride [25] and higher alkylboric anhydrides.[26] Ammonia and trimethylamine formed addition products without destruction of the trimeric character. The ammoniates had the formulæ $(BMeO)_3,NH_3$ and $(BMeO)_3,2NH_3$, the first being stable and the second unstable. The only trimethyl-aminate was $(BMeO)_3,NMe_3$, and this was a fairly stable solid, capable of sublimation in a vacuum. Burg suggests a cyclic structure for the anhydride, similar to the structure of $B_3N_3H_6$, but made up of alternate BMe groups and oxygen atoms. In the

[22] H. I. Schlesinger, N. W. Flodin, and A. B. Burg, *J. Amer. Chem. Soc.*, 1939, **61**, 1078.

[23] *Ibid.*, 1940, **62**, 2228.

[24] H. R. Snyder, J. A. Kuck, and J. R. Johnson, *ibid.*, 1938, **60**, 105.

[25] C. R. Kinney and D. F. Pontz, *ibid.*, 1936, **58**, 197.

[26] H. R. Synder, J. A. Kuck, and J. R. Johnson, *loc. cit.*, ref. (24).

mono-addition compounds there are co-ordinate links from nitrogen to one boron atom, and to explain the unstable diammoniate, the conception of hydrogen bonding is invoked.

In the course of attempts to use boron trifluoride to produce addition compounds with methylboric anhydride, it was found that this reagent causes a breakdown of the trimer according to the (idealised) equation $(BMeO)_3 + 2BF_3 \longrightarrow BMeF_2 + B_2O_3$. The new compound, methylboron fluoride, $BMeF_2$ (b. p. $- 62 \cdot 3°$; m. p. $- 130 \cdot 5°$), is obtained in good yield in this reaction, and by an analogous cleavage of dimethylboric anhydride a second product, dimethylboron fluoride, BMe_2F (b. p. $- 42 \cdot 2°$; m. p. $- 147 \cdot 4°$) is obtained. The discovery of these two substances has completed the series of methylated boron fluorides BF_3, $BMeF_2$, BMe_2F, and BMe_3.

A new and potentially very important link between organic chemistry and the chemistry of the boron hydrides has been established in a recent study by H. C. Brown, H. I. Schlesinger, and A. B. Burg [27] of the reactions of diborane with organic compounds containing a carbonyl group. Certain simple molecules only were used, the first being acetaldehyde, which gave good yields of the new compound diethoxyborine : $4CH_3 \cdot CHO + B_2H_6 = 2BH(OEt)_2$. This, like its homologue dimethoxyborine, decomposes on standing into diborane and the trialkyl borate. It is readily hydrolysed to 1 mol. of boric acid, 1 mol. of hydrogen, and 2 mols. of ethyl alcohol per mol. of the compound. With acetone the main reaction product is di*iso*propoxyborine : $4COMe_2 + B_2H_6 = 2BH(OPr^\beta)_2$. The reaction with trimethylacetaldehyde was examined in order to determine whether enolisation plays any part in these processes, but the result was similar to that with acetaldehyde or acetone, as the following equation shows :

$$4CMe_3 \cdot CHO + B_2H_6 = 2BH(O \cdot CH_2 \cdot CMe_3)_2$$
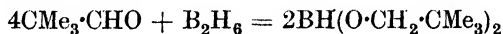
With methyl formate the only products which could be isolated were dimethoxyborine and methyl borate, and it was supposed that the latter was formed together with diborane by disproportionation of dimethoxyborine. The reaction with ethyl acetate was similar, but no reaction was observable between diborane and acetyl chloride, carbonyl chloride, or chloral. In the course of these studies it was pointed out that there was a certain correlation between the ability of the carbonyl group to react with diborane and the stability of the boron trifluoride addition compound which is formed by those substances containing a carbonyl group.

A novel type of boron hydride derivative has been described

[27] *J. Amer. Chem. Soc.*, 1939, **61,** 673.

recently,[28] *viz.*, AlB_3H_{12}, formed by treatment of trimethylaluminium with excess of diborane at temperatures up to 80°. This substance melts at $-64.5°$, has a vapour pressure at 0° of 119 mm., and an extrapolated b. p. of 44°. It undergoes slow polymerisation in the liquid state at room temperature. The reactions have so far been reported on only in a preliminary manner, but with methyl ether the compound AlB_3H_{12},Me_2O results, while with ammonia a series of products containing up to 4 mols. of ammonia is obtained. With trimethylamine there is again a mixture of products, one of these being borine trimethylamine. The authors also mention the interesting fact that diborane reacts with alkyls of metals other than aluminium, giving in some cases alkyldiboranes and also other as yet unidentified products.[28a]

Up to this point the experimental work reviewed has been of interest primarily from the point of view of preparative chemistry, but in the last ten years there has also been a considerable output of research of a more physical character bearing on the question of the structure of the boron hydrides. It was in 1931 that A. Stock and R. Wierl [29] first established by electron-diffraction measurements that the compound $B_3N_3H_6$ has a hexagonal structure. This pioneer investigation has been followed up by S. H. Bauer, and to-day we know the shapes and dimensions of a fair number of the compounds to which reference has already been made.[30]

Electron-diffraction photographs obtained from diborane are very similar to those from ethane and are incompatible with an ethylene-like model.[31] The B–B and B–H bond distances are 1.86 ± 0.04 A. and 1.27 ± 0.03 A., respectively, the valency angle being tetrahedral within 3°. For this model G. N. Lewis [32] has suggested that there might be six electron-pair bonds resonating among seven positions, each bond having six-sevenths single-bond and one-seventh no-bond character. This structure would be stabilised by the resonance energy of the molecule among its seven forms. The above bond distances are larger than the respective single-bond

[28] H. I. Schlesinger, R. T. Sanderson, and A. B. Burg, *J. Amer. Chem. Soc.*, 1939, **61**, 536.

[28a] Recent publications (H. I. Schlesinger, R. T. Sanderson, and A. B. Burg, *J. Amer. Chem. Soc.*, 1940, **62**, 3421; H. I. Schlesinger and H. C. Brown, *ibid.*, p. 3429; A. B. Burg and H. I. Schlesinger, *ibid.*, p. 3425; J. Y. Beach and S. H. Bauer, *ibid.*, p. 3440) describe borohydrides of aluminium, lithium, and beryllium.

[29] *Z. anorg. Chem.*, 1931, **203**, 228.

[30] See also L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, 1939.

[31] S. H. Bauer, *J. Amer. Chem. Soc.*, 1937, **59**, 1096; T. F. Anderson and A. B. Burg, *J. Chem. Physics*, 1938, **6**, 586.

[32] *Ibid.*, 1933, **1**, 17.

values of 1·76 and 1·18 A., a result which is in keeping with Lewis's suggestion. L. Pauling [33] points out, however, that one-electron bond structures also contribute to the resonance effect.

The electron-diffraction investigation of the structures of tetraborane, B_4H_{10}, and pentaborane, B_5H_{11}, showed that the first of these substances has a butane-like structure with B–B and B–H bond distances of 1·84 ± 0·04 and 1·28 ± 0·03 A., respectively.[34] The hydride B_5H_{11} resembles pentane or *iso*pentane in its structure and has B–B and B–H bond distances of 1·81 ± 0·03 and 1·26 ± 0·03 A., respectively. In each of these hydrides Bauer's results indicate that there is free rotation about the boron–boron bond. There are four electrons less than the number needed to provide one electron pair for each bond, and the interatomic distances are in keeping with the hypothesis of resonance among structures of the Lewis type and structures with four one-electron bonds.

The hydride B_5H_9 was found by S. H. Bauer and L. Pauling [35] to have the cyclic structure (I) with the following interatomic distances : B–B, 1·76 ± 0·02 ; B–H, 1·17 ± 0·04 a.

(I.)   (II.)
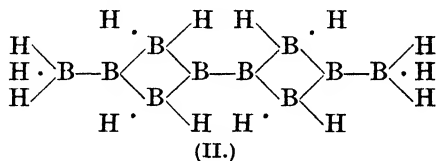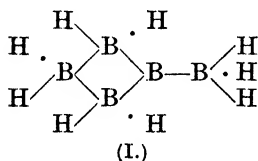
Here again there is believed to be resonance, and the same is likely to be true of the hydrides B_6H_{10} and $B_{10}H_{14}$, which have not, however, been examined experimentally. The structure (II) has been suggested for $B_{10}H_{14}$, with the modification that the electron deficit is not localised in certain singlet linkages, but is distributed throughout the molecule.

Reference has been made already to the structure of triborine-triamine, but this substance was re-examined by S. H. Bauer.[36] The benzene-like form was confirmed, and the B–N distances found to be 1·44 ± 0·02 a. The compound B_2H_7N, to which reference has already been made, was likewise investigated and was assigned

(III.)
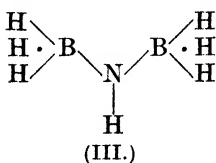
the structure (III), with a B–N bond distance of 1·56 ± 0·03 a., which is close to the single-bond value of 1·59 a. Bauer's observations do not differentiate conclusively between the forms $BH_3 \cdot NH \cdot BH_3$ and $BH_2 \cdot NH_2 \cdot BH_3$, but they establish definitely the existence of the B–N–B unit, the angle of which is tetrahedral within 4°.

[33] *Op. cit.*   [34] S. H. Bauer, *J. Amer. Chem. Soc.*, 1938, **60**, 805.
[35] *Ibid.*, 1936, **58**, 2403.   [36] *Ibid.*, 1938, **60**, 524.

Borine carbonyl and borine trimethylamine have also been examined by the electron-diffraction method.[37]   The former is found to have the B–C–O group arranged linearly, with the hydrogen atoms completing the tetrahedron round the boron (B–H, $1\cdot20 \pm 0\cdot03$; B–C, $1\cdot57 \pm 0\cdot03$; C–O, $1\cdot13 \pm 0\cdot03$ a.); and the latter has a similar structure (B–N, $1\cdot62 \pm 0\cdot15$; N–C, $1\cdot53 \pm 0\cdot06$ a.), which, together with that of borine carbonyl, is discussed by Bauer in terms of the theory of resonance.

H. J. E.

3. FLUORINATION OF INORGANIC COMPOUNDS.

This section of the Report contains a summary of recent publications on the fluorination of inorganic halogen compounds. Although a number of fluorinating agents have been used in the past, attention has hitherto been directed mainly to the preparation of fully fluorinated substances.   A feature of the more recent research in this field has been the successful production of compounds containing fluorine with other halogen atoms.

The fluorinating agent most commonly employed is antimony trifluoride.   It was first introduced by F. Swarts towards the end of last century for the treatment of organic halogen compounds, and has since been widely used for this purpose.   Its general applicability in the field under discussion was first emphasised by H. S. Booth and C. F. Swinehart,[1] who have since studied its reaction with a considerable number of inorganic chloro- and bromo-compounds.   Antimony trifluoride may be used either alone or in conjunction with antimony pentachloride or bromine as a catalyst. The general procedure in performing a fluorination is very simple and consists of heating the halogen compound to be fluorinated with the antimony compound and the catalyst.   Ease of fluorination varies from one compound to another, and it may be necessary to carry out the reaction under pressure in order to attain the needed temperature.   Booth has studied in detail the conditions for replacing part only of the halogen initially present by fluorine, and also the methods of separation of the complex mixtures of fluorinated products which often result, and his publications should be consulted in this connexion for experimental details.

The fluorination of trichlorosilane was the first reaction studied by H. S. Booth and W. D. Stillwell.[2]   The products isolated were : $SiHF_3$ (b. p. $- 97\cdot5°$), $SiHF_2Cl$ (b. p. approx. $- 50°$), and $SiHFCl_2$ (b. p. $- 18\cdot4°$).   The first had been prepared by O. Ruff and

[37] S. H. Bauer, *J. Amer. Chem. Soc.*, 1937, **59**, 1804.
[1] *Ibid.*, 1932, **54**, 4750.   [2] *Ibid.*, 1934, **56**, 1531.

C. Albert [3] by the action of stannic fluoride or titanic fluoride on trichlorosilane. Silicon tetrachloride, when treated in a similar way with antimony trifluoride, gave the compounds SiF_4 (b. p. $-95\cdot7$), SiF_3Cl (b. p. $-70\cdot0°$), SiF_2Cl_2 (b. p. $-32\cdot2°$), and $SiFCl_3$ (b. p. $12\cdot2°$).[4] Germanium tetrachloride gave GeF_4, GeF_3Cl (b. p. $-20\cdot3°$), GeF_2Cl_2 (b. p. $-2\cdot8°$), and $GeFCl_3$ (b. p. $37\cdot5°$).[5] In their general chemical behaviour these substances are intermediate between the tetrachlorides and the tetrafluorides. The chlorofluoro-derivatives of monogermane show a marked tendency to dispro-portionate into germanium tetrafluoride and tetrachloride.

Partly chlorinated silicon hydrides may also be fluorinated by means of antimony trifluoride, and from SiH_3Cl and SiH_2Cl_2 the fluorides SiH_3F (b. p. $-98°$) and SiH_2F_2 (b. p. $-77\cdot5°$) have been obtained.[6] W. C. Schumb and E. L. Gamble [7] were successful in fluorinating hexachlorodisilane completely by reaction with zinc fluoride at 50—$60°$, although hexachloroethane does not exhibit a comparable reaction. The product, Si_2F_6 (v. p. $= 1$ atm. at $-19\cdot1°$), undergoes a mildly explosive reaction with chlorine when the containing vessel is heated locally,[8] resulting in disruption of the Si–Si bond and the formation of SiF_4, SiF_3Cl, SiF_2Cl_2, and probably also traces of $SiFCl_3$. W. C. Schumb and H. H. Anderson [9] have prepared SiF_3Br (b. p. $-41\cdot7°$), SiF_2Br_2 (b. p. $13\cdot7°$), and $SiFBr_3$ (b. p. $83\cdot8°$). The first two of these compounds are formed together with SiF_4 in the reaction between bromine and hexafluoro-disilane. Antimony trifluoride reacts with silicon tetrabromide without a catalyst, and also yields the three mixed halides. It is noteworthy that the fluorinating reaction of silver fluoride in this instance is recorded as being too violent and that of titanium tetra-fluoride too slow.

Fluorochlorobromides of silicon have also been described by Schumb and Anderson,[10] the compounds isolated being $SiFClBr_2$ (b. p. $59\cdot5°$) and $SiFCl_2Br$ (b. p. $35\cdot4°$). Three methods of prepar-ation were used, viz., the partial fluorination of the silicon chloro-bromides $SiClBr_3$ and $SiCl_2Br_2$, the chlorination of silicon fluoro-tribromide ($4SiFBr_3 + 3Cl_2 = 2SiFClBr_2 + 2SiFCl_2Br + 3Br_2$), and the action of antimony trichloride on silicon fluorotribromide, resulting in partial replacement of bromine by chlorine.

The fluorination of a variety of phosphorus halides has also been

[3] *Ber.*, 1905, **38**, 53, 2222.
[4] H. S. Booth and C. F. Swinehart, *J. Amer. Chem. Soc.*, 1935, **57**, 1333.
[5] H. S. Booth and W. C. Morris, *ibid.*, 1936, **58**, 90.
[6] A. G. Maddock, H. J. Eméleus, and C. Reid, *Nature*, 1939, **144**, 328.
[7] *J. Amer. Chem. Soc.*, 1932, **54**, 583.
[8] W. C. Schumb and E. L. Gamble, *ibid.*, p. 3943.
[9] *Ibid.*, 1936, **58**, 994.   [10] *Ibid.*, 1937, **59**, 651.

exhaustively studied by Booth and his collaborators, the m. p.'s and b. p.'s of certain new compounds obtained being tabulated below.

Parent halide.	Deriv- ative.	M. p.	B. p.	Parent halide.	Deriv- ative.	M. p.	B. p.
PCl_3 [1]	PF_3	$-151 \cdot 5°$	$-101 \cdot 1°$	$POBr_3$ [4]	POF_2Br	$- 84 \cdot 8°$	$30 \cdot 5°$
	PF_2Cl	$-164 \cdot 8$	$- 47 \cdot 3$		$POFBr_2$	$-117 \cdot 2$	$110 \cdot 1$
	$PFCl_2$	$-144 \cdot 0$	$13 \cdot 85$	$PSCl_3$ [5]	PSF_3	$-148 \cdot 8$	$- 52 \cdot 3$
PBr_3 [2]	PF_2Br	$-135 \cdot 8$	$- 16 \cdot 1$		PSF_2Cl	$-155 \cdot 2$	$6 \cdot 3$
	$PFBr_2$	$-115 \cdot 0$	$74 \cdot 8$		$PSFCl_2$	$- 96 \cdot 0$	$64 \cdot 7$
$POCl_3$ [3]	POF_3	$- 39 \cdot 4$	$- 39 \cdot 8$				
	POF_2Cl	$- 96 \cdot 4$	$3 \cdot 1$				
	$POFCl_2$	$- 80 \cdot 1$	$52 \cdot 9$				

[1] H. S. Booth and A. R. Bozarth, *J. Amer. Chem. Soc.*, 1939, **61**, 2927.

[2] H. S. Booth and S. G. Frary, *ibid.*, p. 2934.

[3] H. S. Booth and F. B. Dutton, *ibid.*, p. 2937.

[4] H. S. Booth and C. G. Seegmiller, *ibid.*, p. 3120.

[5] H. S. Booth and M. C. Cassidy, *ibid.*, 1940, **62**, 2369.

In the majority of these reactions antimony trifluoride in conjunction with a catalyst has been employed. It is notable, however, that Booth has found calcium fluoride to be a satisfactory fluorinating agent. This material has also been employed for the fluorination of aliphatic halogenated hydrocarbons; [11] it is prepared in pellet form and packed into a heated tube, through which the vapour to be fluorinated is passed. There is no reason to suppose that these would be the only satisfactory fluorinating agents. Thus, for example, zinc fluoride will fluorinate phosphorus tri- or penta-chloride completely and, were it desired to limit the extent of reaction, there is little doubt that the intermediates could be isolated.

An interesting reaction of the tervalent phosphorus fluorochlorides is the addition of halogens : PF_3, PF_2Cl, and $PFCl_2$ all react with chlorine or bromine, forming compounds, which, however, tend to disproportionate. The compounds PF_2Br and $PFBr_2$ also show a considerable tendency to disproportionate.

The partial fluorination of sulphur halides by the methods under discussion has not been described, but interesting results have been obtained with sulphuryl chloride and thionyl chloride. Treatment of sulphuryl chloride at 6 atm. with antimony trifluoride and pentachloride gives the fluorochloride SO_2FCl (m. p. $- 124 \cdot 7°$, b. p. $7 \cdot 1°$) as the sole product.[12] Sulphuryl fluoride itself, although not formed in this reaction, is formed by the interaction of sulphur dioxide and fluorine [13] or by the action of heat on barium fluorosulphonate.[14] The fluorochloride is intermediate in chemical reactivity between SO_2Cl_2 and SO_2F_2. Thionyl chloride with the

[11] E. I. du Pont de Nemours & Co., F.P. 730874, 1932.

[12] H. S. Booth and C. V. Herrmann, *J. Amer. Chem. Soc.*, 1936, **58**, 63.

[13] H. Moissan and P. Lebeau, *Compt. rend.*, 1901, **132**, 374.

[14] M. Trautz and K. Ehrmann, *J. pr. Chem.*, 1935, **142**, 79.

same reagent yields thionyl fluoride and the fluorochloride SOFCl (m. p. $-139.5°$, b. p. $12.2°$).[15]

Fluorination of polymerised phosphonitrile chlorides has been accomplished with the aid of lead fluoride. The polymer $(PNCl_2)_3$ reacts with lead fluoride at $130—340°$, and by fractional distillation of the product the compound $P_4N_4Cl_2F_6$ (b. p. $105.8°$) is obtained.[16] The compound $P_4N_4Cl_4F_4$ (b. p. $130.5°$) has also been isolated from the products of this reaction, and it has been observed that its degree of dissociation when heated is less than that of $P_4N_4Cl_2F_6$ and much greater than that of $P_4N_4Cl_8$, showing that progressive replacement of chlorine by fluorine diminishes the stability of the polymer. When heated under pressure at $100°$, $P_4N_4Cl_4F_4$ is transformed into a rubber-like mass, which decomposes when heated to $250—400°$, giving $P_3N_3Cl_2F_4$ (b. p. $115—117°$) and $P_3N_3Cl_4F_2$ (b. p. $140—142°$).[17]

H. J. E.

4. THE SEPARATION OF ISOTOPES BY THERMAL DIFFUSION.

Thermal Diffusion in Gases.

In the *Annual Report* for 1938 O. J. Walker [1] referred briefly to the application of the principle of thermal diffusion to the separation of isotopic gas mixtures. Very promising separations of the isotopes of some of the lighter elements have since been obtained by this method, and there is no apparent reason why it should not be applied successfully to heavier elements for which efficient chemical or physical methods of isotope separation are not yet available. Some forty papers dealing with this application of thermal diffusion have appeared during the last two years, and the subject merits a separate section of this Report.

It was shown by D. Enskog [2] that the application of a temperature gradient to a gaseous mixture of molecules of different mass should produce a small gradient in the relative concentrations of the constituents; this effect cannot be accounted for by simple kinetic theory, but is explained by a detailed study of the transport equations for a gas mixture.[3] According to Enskog's theory the heavier molecules tend, in general, to diffuse towards the region of lower temperature, and a transport of these molecules continues

[15] H. S. Booth and F. C. Mericola, *J. Amer. Chem. Soc.*, 1940, **62**, 640.

[16] O. Schmitz-Dumont and H. Külkens, *Z. anorg. Chem.*, 1938, **238**, 189.

[17] O. Schmitz-Dumont and A. Braschos, *ibid.*, 1939, **243**, 113.

[1] P. 140.   [2] *Physikal. Z.*, 1911, **12**, 56, 533.

[3] See ref. (2), and L. J. Gillespie, *J. Chem. Physics*, 1939, **7**, 530; S. P. Frankel, *Physical Rev.*, 1940, [ii], **57**, 661.

until the purely *thermal* diffusion process is balanced out by the effect of ordinary diffusion, which tends to re-establish uniformity. of concentrations throughout the mixture.   A similar process produces a corresponding enrichment of the lighter molecules in the region of higher temperature.   The existence of thermal diffusion was predicted independently by S. Chapman,[4] and confirmed experimentally with mixtures of carbon dioxide and hydrogen by Chapman and F. W. Dootson.[5]   The mixtures were confined in two bulbs maintained at different temperatures (T_1, T_2) and joined by a short connecting tube, and after attainment of equilibrium the changes of concentration due to thermal diffusion were determined by isolation and analysis of the contents of each bulb.   Other mixtures have been studied by similar methods.[6]   In the case of a binary mixture the difference of relative concentrations in the two bulbs may be represented by the difference in mol.-fraction of either constituent, which is given by

$$\Delta\lambda = k_T \log_e (T_2/T_1) \quad . \quad . \quad . \quad . \quad (1)$$

k_T is the *coefficient of thermal separation*, which in an isotopic mixture containing two species of molecule (mol.-fractions λ_1, λ_2) is equal to $\alpha\lambda_1\lambda_2$; α is the *thermal diffusion constant*.   If the gas molecules were perfect elastic spheres of molecular weight M_1, M_2, α would be $105(M_2 - M_1)/118(M_2 + M_1)$ (cf. Enskog's theory[7]), but owing to the imperfect behaviour of real gas molecules the experimental values of α are usually rather less than half the values calculated from the Enskog expression.   Equation (1) also gives the difference of the concentrations established at the surfaces of parallel plates enclosing a binary gas mixture, the plates being held at the temperatures T_1 and T_2.   Inspection of the expressions given shows that k_T is relatively small in isotopic mixtures, particularly if the abundance of one of the isotopic species is low; the values of $\Delta\lambda$ obtained by simple thermal diffusion are consequently too small to be of practical value for efficient isotope separations.   It has been calculated[8] that the separation of 20% $^{13}CH_4$ from normal methane (which contains 1·1% of $^{13}CH_4$) would require a group of 810 cells connected in series, each cell consisting of a horizontal plate heated to 500° K. situated 1 cm. above a parallel plate cooled

[4] *Phil. Trans.*, 1917, *A*, **217**, 115.   [5] *Phil. Mag.*, 1917, **33**, 248.
[6] For bibliography, see T. L. Ibbs, *Physica*, 1937, **4**, 1133; also B. E. Atkins, R. E. Bastick, and T. L. Ibbs, *Proc. Roy. Soc.*, 1939, *A*, **172**, 142; N. G. Schmahl and J. Schewe, *Z. Elektrochem.*, 1940, **46**, 203.   The separation of isotopic mixtures (methane and neon) has been studied by this method by A. O. Nier, *Physical Rev.*, 1939, [ii], **56**, 1009; 1940, [ii], **57**, 338.
[7] See W. H. Furry, R. C. Jones, and L. Onsager, *ibid.*, 1939, [ii], **55**, 1083.
[8] J. W. Westhaver and A. K. Brewer, *J. Chem. Physics*, 1940, **8**, 314.

to 300° K.; the power consumption of such a system, all losses being neglected, would be 880 kilowatt hours per g. of $^{13}CH_4$ recovered at 20% concentration.   It is clear from this example that some means of increasing the effectiveness of the thermal diffusion process must be employed if reasonable isotope separations are to be obtained.

A simple means of enhancing the effect of thermal diffusion has been described by K. Clusius and G. Dickel,[9] who discovered the method while tracing the cause of some unexpected demixing effects in gases.   In the parallel-plate thermal diffusion cell pictured, the concentration changes occur without intervention of convection currents, which are deliberately avoided by maintaining the upper plate at the higher temperature. If the apparatus is turned through a right angle, bringing the plates into a vertical plane as shown in section in the figure, a convection current develops in the manner indicated by the arrows.   This current does not prevent the normal thermal diffusion process from establishing a concentration gradient in the direction AB; the gas at A, which is being carried upwards, therefore contains a higher concentration of the lighter molecules than the descending current of gas at B.   The result of the combined thermal diffusion and convection processes is con-

sequently an upward transport of the lighter species of molecule, with a corresponding downward transport of the heavier species; this causes a second concentration gradient to develop in the direction CD.   The transport must clearly continue as long as a difference of concentrations is maintained between A and B, and a considerable concentration gradient may ultimately develop along CD, even though the changes due to pure thermal diffusion along AB are very small; the factor limiting the magnitude of the vertical gradient is not the smallness of the thermal diffusion effect, but the tendency for ordinary diffusion, with some remixing of the gas by the convection currents, to re-establish uniform concentrations.   If the height of the apparatus is large in comparison with the distance between the plates, the opposing effects are relatively small, and considerable enrichments of the respective constituents of the gas mixture are produced at the top and the bottom of the apparatus.
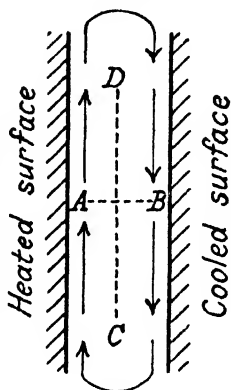
[9] *Naturwiss.*, 1938, **26**, 546, and ref. (13).   See also A. Bramley and A. K. Brewer, *Physical Rev.*, 1939, [ii], **55**, 590; *J. Chem. Physics*, 1939, **7**, 553.

The mathematical theory of the combined thermal diffusion–convection process, although complex, has been studied in some detail.[10]   The results confirm that large separations of gas mixtures should be obtainable, provided that the gas pressure, temperature difference, and distance between the heated and cooled surfaces are suitably chosen; optimum values, which vary with the particular mixture, exist for these three variables.   The separation ultimately attained when the transport process reaches equilibrium with the competing effects increases with the height of the apparatus, but the time required to reach the equilibrium separation also increases.

The apparatus used by Clusius and Dickel[9] to study the process described above consisted of a vertical glass tube 65—290 cm. in length and about 1 cm. in diameter, which was cooled on the outside by running water; an electrically heated platinum or nichrome wire was run along the axis of the tube.   This method of construction reproduces the conditions of the figure in a very simple manner, with the parallel surfaces in the form of concentric cylinders.   The same design has been adopted for all the " thermal diffusion columns " used for gas mixtures, although some workers prefer a rigid, internally heated, inner tube to an axial heating wire; the former arrangement has the advantage that a greater volume of gas can be accommodated in the column for a given distance between the surfaces.

In preliminary experiments Clusius and Dickel[9] demonstrated the effectiveness of their method by rapid and nearly complete separations of bromine vapour–helium and carbon dioxide–hydrogen mixtures.   Definite isotope separations were then obtained by using columns 2·6—2·9 m. in height, with a temperature difference (ΔT) of 600° between the wire and the cooled tube.   Pure neon (atomic weight 20·18) gave a " heavy " fraction, for which a gas-density balance gave an atomic weight of 20·68, and a mass-spectrographic analysis by J. Mattauch showed that the abundances of ^{20}Ne, ^{21}Ne, and ^{22}Ne had been changed from 90·0, 0·3, and 9·7% to 68·4, 0·6, and 31·0%, respectively.   A heavy fraction obtained from hydrogen chloride contained chlorine of atomic weight 35·56, i.e., 0·1 unit above the normal value; this atomic weight was determined chemically by O. Hönigschmid and (Frau) F. Hirschbold-Wittner.[14]   Many previous attempts have been made to separate the chlorine

[10] See ref. (7); L. Waldmann, *Naturwiss.*, 1939, **27**, 230; *Z. Physik*, 1939, **114**, 53; W. van der Grinten, *Naturwiss.*, 1939, **27**, 317; J. Bardeen, *Physical Rev.*, 1940, [ii], **57**, 35; **58**, 94. The following papers deal with the calculation of α : H. Brown, *Physical Rev.*, 1940, [ii], **57**, 242; **58**, 661; R. C. Jones, *ibid.*, p. 111; R. C. Jones and W. H. Furry, *ibid.*, **57**, 547.

isotopes, but atomic weight displacements greater than approximately 0·05 unit (reached by W. D. Harkins by diffusion of hydrogen chloride through porous diaphragms [11]) have not hitherto been obtained. The Clusius and Dickel method is thus remarkably efficient in view of the simplicity of the apparatus.

The preliminary results just described led Clusius and Dickel to attempt a complete separation of the chlorine isotopes,[12] using a system of diffusion columns of much greater length; hydrogen chloride was again used as the " carrier gas." In order to avoid the constructional difficulties and lack of flexibility associated with a single long column, the diffusion apparatus was built up from a number of units 6—9 m. in length. The bottom of each unit was connected to the top of the next by a closed loop of tubing heated electrically on one side so that the gas in the joined ends of the columns was continuously mixed by a convection current. Clusius and Dickel [13] have considered in some detail the arrangement and use of apparatus consisting of a succession of diffusion columns. In such systems a progressive reduction in the diameters of the columns results in increased efficiency, since by this means the rate of transport of the constituent undergoing enrichment in the mixture can be made uniform throughout the apparatus. In the work on hydrogen chloride five different arrangements of units were tried. The highest contents of $H^{37}Cl$ were obtained in a system consisting of columns 7, 9, 6, 6, and 8 m. in length, connected in series; an 18-l. reservoir was inserted in the convective mixing tube between the 7-m. and the 9-m. column to provide a suitably large supply of hydrogen chloride at atmospheric pressure. The columns had an internal diameter of 8·4 mm. (9-m. tube, 12·8 mm.), and heating was effected with 0·4-mm. platinum wires spaced from the column walls by perforated platinum washers at 60-cm. intervals. The wires were heated to approximately 690°. To hasten the attainment of equilibrium some hydrogen chloride enriched in $H^{37}Cl$ in previous experiments was introduced into the " heavy " end of the apparatus at the commencement of the run. After continuous operation for 17 days, 8 c.c. of the heavy hydrogen chloride were removed daily in a gas pipette, and after a further 20 days gas-density measurements on the same daily yield showed its chlorine content to have an atomic weight of 36·98. A concordant value (36·956) was subsequently obtained by chemical atomic-weight determinations of greater accuracy.[14] The atomic weight of ^{37}Cl

[11] W. D. Harkins and F. A. Jenkins, *J. Amer. Chem. Soc.*, 1926, **48**, 58; W. D. Harkins and C. E. Broeker, *Z. Physik*, 1928, **50**, 537.
[12] *Z. physikal. Chem.*, 1939, *B*, **44**, 451.   [13] *Ibid.*, p. 397.
[14] O. Hönigschmid and (Frau) F. Hirschbold-Wittner, *Z. anorg. Chem.*, 1939, **242**, 222.

being assumed to be 36·968, the enriched gas contained 99·4% of $H^{37}Cl$.

As normal hydrogen chloride contains 75·7% of $H^{35}Cl$, the separation of light hydrogen chloride was relatively easy, and it was found that the " light " end of the apparatus just described yielded 96% $H^{35}Cl$. The enrichment was increased further by using the 6, 6, and 8-m. columns in series, with an 8-l. reservoir of normal hydrogen chloride at the " heavy " end of the group; the columns proper were filled initially with partly enriched gas (atomic weight of chlorine, 35·17) from earlier experiments. After four days the light hydrogen chloride gave a densimetric atomic weight of 34·98, and in a further 14 days the aggregate of 28-c.c. portions of gas withdrawn daily gave a chemical atomic weight of 35·021 for its chlorine content; on reducing the daily withdrawal of gas to 16 c.c. the atomic weight fell to 34·979, corresponding to $H^{35}Cl$ of 99·6% purity.[14]

The separation of the isotopes of chlorine in a practically pure state has thus been effected by an efficient and reasonably economical method. The energy required for the separation of the isotopic species in 1 g. of normal hydrogen chloride, in the apparatus described, is $3·7 \times 10^{10}$ g.-cals., representing an efficiency of 9×10^{-9}. The efficiency of the electrolytic separation of deuterium oxide (which admittedly has to be enriched from a much lower abundance) is of the same order, viz., 2×10^{-8}. The apparatus used by Clusius and Dickel could easily be rendered entirely continuous in operation, and large quantities of the enriched gases could be accumulated in a moderate length of time.

Clusius and Dickel, indicating the practical possibility of separating ^{35}Cl free from the heavier isotope, have suggested an interesting use for the separated product;[13] a mass-spectrographic comparison of the atomic weights of ^{18}O and ^{35}Cl, together with a chemical determination of the silver equivalent of ^{35}Cl, would afford a value for the conversion factor for the chemical and the physical atomic weight scale. Previous values of this ratio have depended on accurate measurement of the oxygen isotope abundance ratio.

A 10-c.c. sample of hydrogen chloride containing about 95% of $H^{35}Cl$ has also been obtained by J. W. Kennedy and G. T. Seaborg,[15] using a single 7·5-m. column with a 12-l. reservoir at the lower end. The sample was used to prove that the neutron-induced radioactivity of chlorine is due to ^{38}Cl. The use of separated isotopes in this manner for the precise identification of artificially radioactive elements opens up another field of use for practical methods of separation.

[15] *Physical Rev.*, 1940, [ii], **57**, 843.

The experiments with chlorine have been described first because they have afforded the only reasonably complete isotope separation yet secured by the thermal diffusion method. An obvious application of the method is to the separation of deuterium from ordinary hydrogen. This is relatively difficult, however, because the ease of separation of an isotopic mixture is roughly proportional to k_T (see above), and k_T becomes small when the abundance of the isotope to be enriched is low. G. T. Seaborg, A. C. Wahl, and J. W. Kennedy [16] have carried out separations of hydrogen, deuterium, and the new radioactive hydrogen isotope, ^3H, with a simple 7·5-m. column. With hydrogen already partly enriched in deuterium, the equilibrium separation was reached in three days with the heated wire at 250°; gas at the top and the bottom of the column then contained 18 and 87% of deuterium, respectively, the separation factor being 30. (The separation factor is the concentration ratio of the molecular species at the bottom of the column divided by the corresponding ratio at the top.) The separation factor for deuterium containing 10^{-11} mol.-fraction of ^3H, under identical conditions was 5, the value rising to 9 with the wire at 800°. If allowance is made, according to theory, for the dependence of the separation factor on the masses of the separated molecules, the values given above for hydrogen–deuterium and deuterium–^3H are concordant; this shows that the separation factor of a thermal diffusion column is the same for moderate and extremely low concentrations of either molecular species, a fact of considerable practical importance in the separation of isotopes of low abundance. With two columns connected in series by the Clusius and Dickel method the total separation factor approximated to the product of the values for the individual columns, but the convective mixing device between the tubes was found to increase the time required to reach equilibrium. Seaborg, Wahl, and Kennedy calculate that installations of one, two, or three 7·5-m. columns would produce 1·1, 37, or 97% deuterium, respectively, from normal hydrogen. Clearly the rate of production of deuterium would be small, as its abundance in the normal mixture is so low.

Considerable attention is being directed to the separation of heavy carbon (^{13}C) by the thermal diffusion method. So far all workers have used methane as the carrier gas for this purpose. W. W. Watson [17] has attempted this separation with two 1-m. columns followed by a 3-m. unit, working continuously and yielding 3 c.c. of heavy gas per hour; fresh normal methane was supplied continuously to the top of the first tube to prevent depletion of the supply of $^{13}CH_4$. With the heated surfaces at 330° this apparatus

[16] *J. Chem. Physics,* 1940, **8,** 639.   [17] *Physical Rev.,* 1939, [ii], **56,** 703.

doubled the normal $^{13}CH_4$ concentration (1·1%). In later work [18] Watson has used standardised 2-m. units constructed round commercial heating elements; two such units gave a 2·77-fold concentration of $^{13}CH_4$, and a series of six should produce a 21-fold enrichment. A. O. Nier,[19] with a 5·5-m. single column filled with methane at the optimum pressure of 46 cm., has obtained 4·57% $^{13}CH_4$, with a possible yield of 148 mg. of the enriched gas per hour. The same column would afford 376 mg. per hour of 3·4% $^{13}CH_4$, using gas at 61 cm. pressure. T. I. Taylor and G. Glockler [20] have described a 10·9-m. column constructed from iron tubing of standard sizes, with which 3·6% $^{13}CH_4$ has been obtained; the time required to reach equilibrium was about 180 hrs., with gas at 28 cm. pressure and $\Delta T = 310°$. This column would yield 9% heavy methane if fresh normal methane were circulated at the top. H. S. Taylor,[21] in describing the results of some preliminary experiments with diffusion columns, states that a 12-m. column used under specified conditions should produce 20% $^{13}CH_4$. The isotopic composition of the methane obtained by all the above workers was determined in a mass spectrometer. No doubt the application of the diffusion method to the carbon isotopes will be further developed in the near future; although the experimental technique is simpler, the results so far obtained are scarcely comparable with those secured by the chemical exchange method,[22] which has yielded 2·5 g. of 25% $Na^{13}CN$ per day in an apparatus containing two exchange units.

R. Fleischmann [23] has obtained enrichments of heavy nitrogen (^{15}N) by the thermal diffusion method. Two 12-m. columns were used separately to produce a quantity of gas containing 9·2% of $^{15}N^{14}N$ from normal nitrogen (0·8% $^{15}N^{14}N$), and in a second stage this enriched gas, in one of the columns, gave 110 c.c. of 18% $^{15}N^{14}N$. Unfortunately no attempt was made to separate the heavy nitrogen from accompanying argon, and its concentration was estimated by an indirect method. A marked enrichment was, however, confirmed by band-spectrum photographs. In the case of nitrogen, the chemical exchange method has afforded much better results, for H. G. Thode and H. C. Urey [24] have obtained material containing up to 70% of ^{15}N.

No work has yet been published on the separation of ^{18}O from oxygen by thermal diffusion, although the method should be applicable in this case. If the process were applied to oxygen gas the

[18] *Physical Rev.*, 1940, [ii], **57**, 899.   [19] *Ibid.*, p. 30.

[20] *J. Chem. Physics*, 1939, **7**, 851; 1940, **8**, 843.

[21] *Nature*, 1939, **144**, 8.

[22] C. A. Hutchinson, D. W. Stewart, and H. C. Urey, *J. Chem. Physics*, 1940, **8**, 532.

[23] *Physikal. Z.*, 1940, **41**, 14.   [24] *J. Chem. Physics*, 1939, **7**, 34.

^{18}O would appear as $^{18}O^{16}O$ molecules, owing to the low abundance. Clusius and Dickel [25] have pointed out, however, that if the wire temperature were sufficiently high the equilibrium $2^{18}O^{16}O \rightleftharpoons$ $^{18}O_2 + {}^{16}O_2$, established in the high-temperature region of the column, would enable $^{18}O_2$ molecules to be separated.

The partial separation of the neon isotopes obtained by Clusius and Dickel has been described above; a somewhat smaller separation has been secured by W. W. Watson.[18] Partial separations have also been effected with krypton and xenon; [26] krypton gave light fractions with atomic weights up to 1·74 units less than the normal value, while heavy and light xenon fractions differing in atomic weight by 1·57 units were obtained. In both separations relatively short columns (5·5 and 2·5 m.), with unusually high wire temperatures (1500°, 1750°), were successfully used. The atomic-weight displacements were determined by a thermal conductivity method, which in the case of xenon is claimed to give results correct to 0·01% with 1 c.c. of gas. The separation of xenon is of special interest in that a parallel enrichment was effected in a series of 12 Hertz diffusion pumps, which were found to be approximately equivalent to a thermal diffusion column only 1 m. long.

Thermal diffusion separations of the isotopes of other elements have not so far been described, although W. Krasny-Ergen [27] has given a specification for a column designed to separate ^{235}U, using uranium hexafluoride as the carrier gas. Considerable interest attaches to the enrichment of this isotope in view of its possible rôle in nuclear chain reactions in uranium. Probably the thermal diffusion column provides the only means yet discovered of enriching such a heavy isotope in appreciable quantities; it appears possible, however, that more success will be achieved in this separation if it can be carried out in the liquid phase (see below).

Although the thermal diffusion constant, α, for a gas mixture is mainly determined by the masses of the molecules, other factors are also involved. This is shown by successful separations of mixtures of gases of approximately equal molecular weight.[28] In carbon dioxide–propane, carbon monoxide–ethylene, and nitrogen–ethylene mixtures the larger species of molecule is enriched at the bottom of the diffusion column, but in carbon dioxide–nitrous oxide the latter gas separates at the bottom. No measurable enrichments were obtained with carbon monoxide and nitrogen. The separations

[25] See ref. (13), p. 449.
[26] W. Groth and P. Harteck, *Naturwiss.*, 1940, **28**, 47; W. Groth, *ibid.*, 1939, **27**, 260.
[27] *Nature*, 1940, **145**, 742.
[28] F. T. Wall and C. E. Holley, jun., *J. Chem. Physics*, 1940, **8**, 348.

recorded were too large to be accounted for by the fractional differences in molecular weight of the two components of each mixture.

Gases vary in their relative efficiency as " carriers " in isotope separations by thermal diffusion, and calculated values of α obtained from viscosity data [29] may be used as a rough guide to the probable suitability of a given gaseous compound for this purpose. The results show, for example, that nitrogen should give better results than ammonia, nitric oxide, or nitrous oxide in the separation of nitrogen isotopes.

Clusius and Dickel [12] have found that the efficiency of a thermal diffusion column is increased by the washers used to space the heating wire from the walls of the tube. A. Bramley and A. K. Brewer [30] have also found that " baffle plates " inserted at intervals along a column increase its separation factor to a considerable extent. These results suggest that improved efficiency may be obtained by changes in the mechanical design of diffusion columns.

Clusius and Dickel [13] have pointed out several applications of the thermal diffusion method outside the field of isotope separations. Certain gases, such as xenon and helium, can be rapidly purified from substances of appreciably different molecular weight. The formation of association compounds in the gas phase can be studied, and suspended particles in fogs and smokes can be separated very effectively. The vapours of azeotropic liquid mixtures should also be separable. It should be emphasised that the thermal diffusion column is an experimental tool of general utility, which should be valuable in effecting separations in which the commoner physical methods of distillation, fractional adsorption, etc., are inefficient or have failed.

Thermal Diffusion in Liquids.

An effect similar to the more recently discovered thermal diffusion process in gases has long been known to exist in solutions and liquid mixtures, in which a temperature gradient produces a small corresponding gradient in the relative concentrations (Ludwig–Soret effect [31]); this effect is now regarded as a consequence of thermal diffusion. With suitable modifications in experimental technique the convective action utilised in the thermal diffusion column for gases should therefore produce correspondingly large separations in liquids. As the thermal diffusion constants for liquids are very much smaller than those obtaining in the gas phase,

[29] H. Brown, *Physical Rev.*, 1940, [ii], **57**, 242.

[30] *J. Chem. Physics*, 1939, **7**, 972.

[31] C. Ludwig, *Wien. Akad. Ber.*, 1856, **20**, 539; C. Soret, *Ann. Chim. Phys.*, 1881, **22**, 293.

the separation process is slower and the optimum distance between the heated and cooled surfaces is smaller (of the order of 0·1—0·25 mm.). Preliminary attempts to apply the new process to liquids were made by H. Korsching and K. Wirtz and by Clusius and Dickel,[32] who successfully separated several solutions and mixtures of organic liquids. A simple glass diffusion column in which visible sedimentation of aqueous copper sulphate and cobalt chloride solutions can be obtained has been described by D. Taylor and M. Ritchie.[33] The first actual isotope separation effected by thermal diffusion in a liquid was obtained by Clusius and Dickel[32] with heavy water; in an apparatus consisting of heated and cooled parallel flat plates enclosing a diffusion space 150 cm. long, 2 cm. wide, and 0·1 mm. thick, a sample of heavy water was separated to concentrations of 62·9 and 64·5% deuterium oxide, respectively, at the top and the bottom, after 8 hours' operation with a temperature difference of 80° between the plates. Korsching and Wirtz [34] have also separated deuterium oxide–water mixtures, in one case in a column only 10 cm. long. Although these separations were obtained under favourable conditions in partly enriched material, they demonstrate the practical possibility of isotope separations in liquids. In spite of the fact that the process is slow, the necessary apparatus is not cumbersome and reasonable quantities of enriched product should be obtainable. In a more detailed paper,[35] Korsching and Wirtz have described suitable types of diffusion column, and indicated methods by which these may be used in successive stages to effect large separations.

The theory of the thermal diffusion column for liquids has been developed by P. Debye,[36] and extended by J. W. Hiby and K. Wirtz [37] to practical types of apparatus. At present the theory is not sufficiently developed to predict whether an isotope separation can be effected in a given liquid; Wirtz [38] has discussed methods of calculating the thermal diffusion constant for a liquid mixture and the possibility of isotope effects, but the problem is complex because various factors connected with the structure of the liquid state are involved.

Dissolved salts containing different isotopes should clearly sediment out at slightly different rates in a diffusion column, and a partial separation of the isotopes should result. A claim to have changed the zinc isotope abundances in zinc sulphate solution by

[32] *Naturwiss.*, 1939, **27**, 110, 148. [33] *Nature*, 1940, **145**, 670.
[34] *Naturwiss.*, 1939, **27**, 367. [35] *Ber.*, 1940, **73**, 249.
[36] *Ann. Physik*, 1939, [v], **36**, 284.
[37] *Physikal. Z.*, 1940, **41**, 77.
[38] *Naturwiss.*, 1939, **27**, 369; *Ann. Physik*, 1939, [v], **36**, 295.

this method remains unsubstantiated.[39]   Hiby and Wirtz [37] have discussed the conditions necessary for this type of separation; its disadvantage is the large change of total concentration which accompanies the selective sedimentation effect.   It may be possible to avoid this in some degree by a suitable choice of solvent.

No doubt the further development of the liquid diffusion column will indicate numerous possible applications, both in isotope separations and in general chemistry.   Several such applications are now in course of examination.[40]

A. J. E. W.

H. J. Eméléus.
A. J. E. Welch.

[39] See ref. (34), and *Z. Elektrochem.*, 1939, **45**, 662.
[40] A. J. E. Welch, unpublished.

CRYSTALLOGRAPHY.

1. INTRODUCTION.

THIS Report has been affected by present circumstances because the contributors are all engaged to a considerable extent on unusual duties which make it difficult for them to collect the necessary material, especially when access to many of the scientific journals is difficult in any case. In spite of this, however, the ground has been covered fairly well, and it is encouraging to note that pure research work is being continued without very much abatement.

As before, the first part of this Report deals with the more physical aspects of X-ray analysis and crystallography. A new phenomenon has recently been engaging a great deal of attention in this field. When X-rays are passed through a stationary crystal, a well-defined series of sharp spots are usually obtained on a photographic plate placed behind the crystal—the well-known Laue pattern; but in certain circumstances other effects can be observed. These are spots of a more diffuse character and disposed in a different way. Their interpretation forms an interesting problem which is being vigorously discussed with a considerable amount of disagreement between different observers. There is no doubt, however, that the phenomena are of importance, and even in the absence of theoretical explanation they can be utilised as an aid to structural work in some cases. The matter is briefly dealt with in Section 2, as well as recent work on melting and crystal structure, and generally on the transition from the liquid to the solid and other states of matter. Section 3 gives a brief account of recent work on hindered rotation about single bonds, which has considerable bearing on these as well as on the more structural topics in this Report.

A proper review of recent work on structural chemistry is always hampered by the somewhat fictitious title of this Report. Liquids can sometimes be disguised as crystals but gases tend to escape, and this year the structural work carried out by electron-diffraction studies will be found in another part of the volume. In Section 4, however, the other main advances in the field of inorganic structures are set out. Two very general works of great importance have appeared during the year. The first of these [1] deals with the general problem of directed valency from the standpoint of group theory and contains a valuable tabulation of spatial arrangements derived

[1] G. E. Kimball, *J. Chem. Physics*, 1940, **8**, 188.

from all possible configurations of the valency electrons on the central atom. In the second work [2] there is a most valuable collection of all the experimental data relating to the spatial arrangements of covalencies, with nearly 400 references to original papers, mainly in the fields of X-ray and electron-diffraction work. It is observed that these arrangements tend to conform to quite a limited number of types, and the attempt is made to relate these types to some familiar property of the atom. This property is the size of the valency group and the number of shared electrons which it contains, together with the number of (unshared) electrons in the preceding group.

These works are reviewed in Section 4, and are followed by an account of recent experimental work on new structures in the inorganic field. These are not as numerous as usual, but contain a number of interesting examples.

New work in the field of organic structures is discussed in Section 5. Circumstances have made it necessary to confine this account chiefly to those new structures which have been completely determined during the year, and although not very numerous they contain some very interesting results. Some of the macrocyclic pigments which were expected to be isomorphous with the phthalocyanines have been shown to possess a different type of crystal structure, but this has not been fully worked out. The detailed analysis of the platinum phthalocyanine structure, obtained in a very direct manner from the intensity data, has been published, and here again the type differs from that of the other phthalocyanines. The difference, however, is one of molecular packing and not, to any appreciable extent, of molecular structure.

Some account is given of two other structures that have been fully determined, the rhombohedral form of acetamide and the dimer of cyanamide, dicyandiamide. In both cases the molecules are relatively simple ones, but crystallographically the structures are complex, and their complete analyses represent a considerable achievement. The interatomic distances can be determined in each case with sufficient accuracy to enable the state of the resonance hybrid to be ascertained. In each case the molecules are held together by an interesting arrangement of hydrogen bonds which have a considerable effect on the stability of the structure.

Much other work on hydrogen bonds has been published during the year, but as this is largely in the form of a general discussion [3] it has not been thought necessary to review the work again here.

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[2] N. V. Sidgwick and H. M. Powell (Bakerian Lecture), *Proc. Roy. Soc.*, *A*, 1940, **176**, 153.

[3] J. M. Robertson, *Trans. Faraday Soc.*, 1940, **36**, 913.

There has also been a certain amount of work on complex polymers, rubber, and proteins, but an account of these subjects must be deferred to a later Report. J. M. R.

2. CRYSTAL PHYSICS : THERMODYNAMICS AND STRUCTURE.

In more normal times, topics for the *Annual Reports* are usually selected so as to give a critical account of recent work, over a period of years. The history of science during the war of 1914—1918 shows that, although the advancement of knowledge may be thrown violently out of balance, important developments do not wait for peace. The choice of subjects in the following pages has therefore been directed to those fields whose development has been rapid, even when a critical review is not yet possible.

Temperature Effects in the Reflection of X-Rays from Crystals.— As described in a previous Report,[1] the normal effect of raising the temperature of a crystal is to increase the amplitude of its lattice vibrations, and hence to decrease the intensity of X-rays reflected by various lattice planes. Renewed attention has recently been given to certain " diffuse spot " reflections [2] exhibited by some crystals, when set up so as to give the familiar Laue reflections. These diffuse reflections are additional to the normal Laue pattern. It was furthermore shown by G. D. Preston [3] that, contrary to the behaviour of Laue spots, they are obtained with monochromatic X-rays, and that their intensity increases with rise in temperature. Diffuse reflections have been reported for single crystals of such varying nature as rock salt, sylvine, diamond, zinc, aluminium,[3] sodium nitrate,[4] benzil,[5] urea nitrate, urea oxalate, sorbic acid, hexamethylbenzene, and α-resorcinol.[6]

The theoretical interpretation of the origin of these diffuse reflections is still under discussion. According to Preston, although the reflections might be due to two-dimensional gratings (*i.e.*, sheets of atoms particularised in some way in the crystal), the intensities are in better agreement, at least in the case of aluminium, with the assumption that the crystals are broken up into groups, probably consisting of an atom and twelve neighbours. The

[1] *Ann. Reports*, 1939, **36,** 155.

[2] A. Guinier, *Compt. rend.*, 1938, **206,** 1641; A. P. Wadlund, *Physical Rev.*, 1938, **53,** 843; A. Taylor and D. Laidler, *Nature*, 1940, **146,** 130.

[3] *Ibid.*, 1939, **143,** 76; *Proc. Roy. Soc.*, 1939, **172,** *A*, 116.

[4] (Sir) C. V. Raman and P. Nilakantan, *Nature*, 1940, **145,** 667; *Proc. Indian Acad. Sci.*, 1940, **11,** *A*, 379.

[5] (Miss) I. E. Knaggs, (Mrs.) K. Lonsdale, A. Müller and A. R. Ubbelohde, *Nature*, 1940, **145,** 820.

[6] (Miss) I. E. Knaggs, (Mrs.) K. Lonsdale, and H. Smith, *ibid.*, **146,** 332.

interatomic distances are supposed to vary slightly from one group to another, and this effect is ascribed to thermal vibrations. An alternative explanation is advanced by W. Zachariasen and his colleagues,[7] following on the work of Faxen. According to these authors, the standing waves in a crystal, formed by the thermal vibrations, give rise to new regularities in the density distribution, and hence to new reflections at higher temperatures. Yet another physical explanation, analogous to the Raman effect for simple molecules, is advanced by Raman and his colleagues.[4]

This diversity of theories makes it clear that with the present experimental information more than one physical cause might be responsible for diffuse reflections in single crystals.[5, 8] Indeed, since crystals can have more than one source of energy, whose increase with rise in temperature will lead to minor modifications in structure,[1] the origin of diffuse spot reflections may not be unique. A geometrical examination of possible groupings of atoms which may be responsible for diffuse reflections has been put forward by (Sir) William Bragg,[9] and has the advantage that the reflections can be discussed without requiring any assumption about the physical cause for such groupings.

The marked temperature dependence of the intensity of diffuse reflections suggests that further experiments will have considerable influence in developing the thermodynamics of crystals.

The Transition from Liquid to Solid.—Owing to the fact that melting is conditioned by the equilibrium between a solid and a liquid state of matter, an account of the transition should properly include some description of recent work on the structure of both the solid and the liquid state. Within the last few years, fresh theories about the liquid state have been almost more abundant than fresh experimental information. A comprehensive description of work on the liquid state is outside the scope of this report, but reference may be made to two recent summaries.[10, 11]

It would not be possible, however, to give an account of modern work on melting, without alluding to two broad lines of experimental research on liquids. The first of these has established that many properties of liquids can be accounted for much better by the assumption that their structure is quasi-crystalline, at any rate in

[7] A. P. Wadlund and W. Zachariasen, *Physical Rev.*, 1938, **53**, 843; *Nature*, 1940, **145**, 1019; W. Zachariasen and S. Siegel, *Physical Rev.*, 1940, **57**, 597, 795.

[8] *Proc. Roy. Soc.*, 1938, **168**, *A*, 302.   [9] *Nature*, 1940, November.

[10] J. A. V. Butler, *Ann. Reports*, 1937, **34**, 75.

[11] N. F. Mott and R. W. Gurney, *Ann. Reports Physical Soc.*, 1938, **5**, 46; *J. Chem. Physics*, 1938, **6**, 222; C. A. Benz and G. W. Stewart, *Physical Rev.*, 1934, **46**, 702.

the neighbourhood of the melting point, than by the assumption, incorporated in van der Waals's famous theory, that the structure of liquids is quasi-gaseous. One of the simplest illustrations of this conclusion is provided by the specific heats, in the neighbourhood of the melting point. For solid mercury, $C_v = 6 \cdot 72$, and for liquid mercury, $C_v = 5 \cdot 90$ cals./mol.[12] This behaviour is not restricted to liquids with simple molecules, since the specific heats of solid and liquid long-chain paraffins are also closely similar.[13, 14]

Other information on the quasi-crystalline structure of liquids includes the Brillouin scattering of monochromatic light by stationary waves in the medium, which gives a broadened central line for gases, a doublet for solids, and a doublet + a central line for liquids.[12] The absorption of ultrasonic waves and high-frequency electromagnetic waves provides further evidence.[15] X-Ray studies on liquids continue to show the roughly similar packing of the molecules, compared with the corresponding solids.[16] Miscellaneous investigations cover work on liquid carbon dioxide,[17] on the structure of molten salts,[18] on the viscosity of liquid metals near the melting point,[19] on thermodynamic evidence for the restricted rotation of molecules in certain liquids,[20] and on some mechanical models for liquids.[21] The general conclusion [22] is that the packing of molecules in most liquids, near their freezing points, is roughly similar to the packing in the corresponding solids, but that any micro-crystals in the liquid do not as a rule comprise more than very few molecules. An alternative description, referred to again below, is that a liquid, near the melting point of the solid, corresponds with a polycrystalline conglomerate in which the individuals have such a large number of defects that its crystalline character is not apparent except in special tests.

[12] P. Debye, *Z. Elektrochem.*, 1939, **45**, 174.

[13] A. R. Ubbelohde, *Trans. Faraday Soc.*, 1938, **34**, 289.

[14] L. Brillouin, *J. Phys. Radium*, 1936, **7**, 153 (see, especially, theoretical discussion).

[15] P. Debye and W. Ramm, *Ann. Physik*, 1937, [v], **28**, 28.

[16] *E.g.*, W. Pierce, *J. Chem. Physics*, 1935, **3**, 266; W. Pierce and D. Macmillan, *J. Amer. Chem. Soc.*, 1938, **60**, 779; H. Sirk, *Z. Physik*, 1934, **89**, 129.

[17] L. H. Borchert, *Physikal. Z.*, 1938, **39**, 156.

[18] E. Miller, *Physical Rev.*, 1940, **57**, 61.

[19] Y. S. Chiong, *Proc. Roy. Soc.*, 1936, **157**, A, 264.

[20] A. R. Ubbelohde, *Trans. Faraday Soc.*, 1939, **35**, 843; R. S. Halford, *J. Chem. Physics*, 1940, **8**, 496; D. Osborne, R. Doescher, and D. Yost, *ibid.*, p. 506; E. Fischer and G. Klages, *Physikal. Z.*, 1939, **40**, 721.

[21] H. Rehaag and H. A. Stuart, *ibid.*, 1937, **38**, 1027; W. Kast and H. A. Stuart, *ibid.*, 1939, **40**, 714; R. Fürth, L. S. Ornstein, and J. M. W. Milatz, *Proc. K. Akad. Wetensch. Amsterdam*, 1939, **42**, 107.

[22] Cf. A. Magat, *Trans. Faraday Soc.*, 1937, **33**, 114; J. Malsch, *Z. Elektrochem.*, 1939, **45**, 813; F. Frank, *Physikal. Z.*, 1938, **39**, 530.

A second broad line of experimental research on liquids refers to work on the formation of crystal nuclei. Evidence for the quasi-crystalline structure of liquids, near their freezing points, emphasises the similarity in packing of molecules in the liquid and the solid state of matter. On the other hand, evidence about the spontaneous formation of crystal nuclei in melts or solutions makes it quite clear that there must also be a marked difference in the arrangement of molecules in the two states. Numerous cases are known of the supercooling of a melt or solution, without any separation of crystals. On the other hand, definitely established cases of the superheating of crystals above their melting point are so rare [23] that they might be described as non-existent. A further peculiarity of spontaneous crystallisation is the tendency for the least stable state to separate preferentially, according to the so-called rule of successive states. Recent examples of the formation of metastable states include zinc sulphide,[24] the precipitation from certain solid solutions on cooling,[25] and the crystallisation of some long-chain compounds from their melts.[26]

A theoretical interpretation of the rules governing melting and crystallisation has been suggested in terms of the thermal fluctuations in the systems.[27]

Experimental evidence for the persistence of crystallisation nuclei above the melting point of the solid,[28] and for various mechanisms which may apply in the spontaneous formation of crystal nuclei,[29] has hardly done more than emphasise the difficulties in studying nucleus formation. The recently discovered influence of an electric field on the location of nuclei in supercooled melts or solutions [30] may help to solve some of the 'experimental difficul-

[23] M. Volmer and O. Schmidt, *Z. physikal. Chem.*, 1937, **35**, *B*, 467.

[24] S. Madigan, *Physical Rev.*, 1937, **51**, 61.

[25] A. J. Bradley, *Proc. Physical Soc.*, 1940, **52**, 80.

[26] J. W. H. Oldham and A. R. Ubbelohde, *Proc. Roy. Soc.*, 1940, **176**, *A*, 50, 65.

[27] A. R. Ubbelohde, *Trans. Faraday Soc.*, 1937, **33**, 1203; G. Borelius, *Ann. Physik*, 1938, [v], **33**, 517; but see F. C. Frank, *Proc. Roy. Soc.*, 1939, **170**, *A*, 182.

[28] V. Danilov and J. Radschenko, *Physikal. Z. Sovietunion*, 1937, **12**, 745; P. Anderson, *Physical Rev.*, 1936, **50**, 386; R. Kaischew, *Ann. Physik*, 1937, [v], **30**, 184; W. L. Webster, *Proc. Roy. Soc.*, 1933, **140**, *A*, 653.

[29] A. T. Jensen, *Z. physikal. Chem.*, 1937, **180**, *A*, 93; A. T. Wahramian and S. A. Alemian, *Acta Physicochim. U.R.S.S.*, 1937, **7**, 95; E. Andronikaschvili, *ibid.*, **6**, 689; G. L. Michnevitsch *et al.*, *Physikal. Z. Sovietunion*, 1938, **13**, 103; V. Danilov and W. Neumark, *ibid.*, 1937, **12**, 313; L. Horn and G. Masing, *Z. Elektrochem.*, 1940, **46**, 109; L. Hamburger, *Chem. Weekblad*, 1938, **35**, 886; I. Sokolov, *Tech. Phys. U.R.S.S.*, **5**, 619; G. Schmid and A. Roll, *Z. Elektrochem.*, 1939, **45**, 769.

[30] W. Rix, *Z. Krist.*, 1937, **96**, 155; C. Hammer, *Ann. Physik*, 1938, [v], **38**, 445; H. C. Hamaker, *Trans. Faraday Soc.*, 1940, **36**, 279; A. R. Ubbelohde, *ibid.*, p. 863.

ties. In connection with the effect of chance dust particles on nucleation, mention may be made of studies on the melting of adsorbed substances [31] and of two-dimensional layers of molecules.[32]

Factors influencing the steady velocity of growth of crystals, once these have reached a sufficient size, are also of importance in determining the transition from liquid to solid. Recent experiments have made some progress in this field.[33]

Melting and Crystal Structure.—The heat of fusion and the melting point of crystals range from very low values, for helium, to very high values, such as are exhibited by certain carbides, and by graphite (m. p. *ca.* 4000° K.).[34] The ratio of the heat of fusion to the melting point, measured on the absolute scale of temperature, gives the entropy of fusion ΔS_f, which is a far more useful quantity in correlating melting with crystal structure. Inspection of the Boltzmann equation for the entropy of fusion,[35] *viz.*, $\Delta S_f = R \log_e W_l/W_s$, suggests that the number of ways, W_s and W_l, of realising the solid and the liquid state might be the same for crystals of similar structure, irrespective of the actual melting point. In parallel with Trouton's rule, which states that the entropy of vaporisation at constant pressure is independent of the boiling point, Richards's rule for solids states that for crystals with similar structure, the entropy of melting is a constant, independent of the actual melting point.[36]

In practice, Richards's rule for the melting of solids is found to have a far narrower scope than Trouton's rule for liquids. The reason for this is that as soon as the number of atoms per molecule increases, the number of degrees of freedom of the molecule likewise increases. Owing to the constraints imposed by the crystal structure, these degrees of freedom are frequently not fully excited in the solid, but may become active on melting, thereby increasing the entropy of fusion. A simple illustration of how this can upset a smooth sequence of melting points can be obtained from a comparison of a

[31] W. A. Patrick and W. A, Kemper, *J. Physical Chem.*, 1938, **42**, 369; W. T. Richards, *J. Amer. Chem. Soc.*, 1932, **54**, 479.

[32] D. Dervichian, *J. Phys. Radium*, 1939, **10**, 333.

[33] J. Michel, *Bull. Soc. chim. Belg.*, 1939, **48**, 105; J. Dubourg and R. Saunier, *Bull. Soc. chim.*, 1938, [v], **6**, 1196; M. Pahl, *Z. physikal. Chem.*, 1938, **184**, 245; D. Mavroska and G. Valensi, *Compt. rend.*, 1939, **208**, 1648, 1727; T. Erdey-Grúz and R. Kardos, *Z. physikal. Chem.*, 1936, **178**, A, 255, 266; W. F. Berg, *Proc. Roy. Soc.*, 1938, **164**, A, 79; U. Hoffmann, *Ber.*, 1939, **72**, 754; H. E. Buckley, *Mem. Manchester Lit. Phil. Soc.*, 1939, **83**, 32.

[34] W. Hume-Rothery, *J. Physical Chem.*, 1940, **44**, 808; J. Bassett, *J. Phys. Radium*, 1939, **10**, 217.

[35] *Ann. Reports*, 1939, **36**, 163.

[36] Cf. A. Eucken, " Energie and Warmeinhalt "; also tabulated data, *Ann. Reports*, 1939, **36**, 159.

range of similar crystals, in which rotation of the molecules occurs in some examples, but not in others.[37]   Abnormally low melting points are usually found in the sequence, when the entropy of melting is high, *i.e.*, when the entropy increase for rotation is included in the entropy of fusion.

When a wider range of crystals is considered, particularly in the case of complicated organic molecules, it is found that the entropy of melting can have almost any value.[38]   Systematic investigations have been carried out chiefly in the case of long-chain polymethylene molecules.   So far as is known,[39] there is no upper limit to the entropy of melting.   Empirical formulæ for the freezing point of various homologous series can be interpreted on the assumption that successive methylene groups make a constant addition to both the heat of fusion and the entropy of fusion.   If n is the number of CH_2 groups, and H and S the respective increments of heat and entropy of fusion, these can be written

$$\Delta H_f = H_0 + nH$$
$$\Delta S_f = S_0 + nS$$

where H_0 and S_0 are constants characteristic of the compound (long-chain paraffin, alcohol, ketone, iodide, etc.).   When these formulæ apply, the melting point $T_m = \Delta H_f / \Delta S_f$ reaches a limiting " convergence temperature " for very high values of n.[40] Some attempt has been made to give a physical interpretation of these equations connecting the entropy and heat of fusion with the number of methylene groups,[41] kinetic arguments being used to describe the melting of chain molecules.   There is evidence that torsional vibrations of the chains play a considerable part in the melting of polymethylene compounds,[26, 42] and rotation may not be entirely free even in the liquid phase.[43]   It is interesting to note that the stiffening of a long chain by conjugation, as in the polyenes,[44] leads to a quite different behaviour on lengthening the chain.   So

[37] W. O. Baker and C. P. Smyth, *J. Amer. Chem. Soc.*, 1939, **61**, 1695.

[38] J. Timmermans, *Bull. Soc. chim. Belg.*, 1935, **44**, B, 17; *J. Chim. physique*, 1938, **35**, 335; *Bull. Acad. roy. Belg.*, 1939, **25**, 417; A. van de Vloed, *Bull. Soc. chim. Belg.*, 1939, **48**, 229.

[39] A. R. Ubbelohde, ref. (20).

[40] J. Timmermans, *Bull. Soc. chim. Belg.*, 1919, **28**, 392.

[41] (Miss) A. M. King and W. E. Garner, *J.*, 1936, 1368.

[42] J. W. H. Oldham and A. R. Ubbelohde, *Trans. Faraday Soc.*, 1939, **35**, 332; A. Müller, *Proc. Roy. Soc.*, 1940, **174**, A, 137; A. Eucken and E. Schroder, *Ann. Physik*, 1939, [v], **36**, 609.

[43] J. S. Koehler and D. M. Dennison, *Physical Rev.*, 1940, **57**, 1006; W. B. Bridgman, *J. Amer. Chem. Soc.*, 1938, **60**, 530.

[44] R. Kuhn and C. Grundmann, *Ber.*, 1936, **69**, 224.

far as has been determined, the melting point continues to rise steeply as the number of carbon atoms increases.

Attempts to derive a statistical theory of melting depend on the devising of a successful model on which to base calculations of the partition functions of the solid and the liquid state. Quite naturally, theories have so far been restricted to the melting of simple atomic lattices, where no degrees of freedom need be considered in the liquid or solid, apart from those connected with the positions of the centres of gravity of the atoms. Considerable success has been achieved with the carefully worked out model due to Lennard-Jones and his colleagues.[45] According to this model, the crystalline state at low temperatures corresponds with a state of complete order of the atoms, all being situated at the specified points or α sites of the crystal lattice. With rise in temperature, some of the atoms can occupy intermediate β sites in the crystal, and the liquid corresponds with an arrangement in which the occupation of β sites preponderates. The presence of empty α sites in this model explains the easy migration of atoms in the liquid, and accounts for its mechanical properties. Although the model is necessarily formalised for the purpose of calculation, successful estimates have been made by its means of the entropy and volume changes on melting the lattices of argon and nitrogen. The heat of fusion has also been calculated. Molecules are treated as equivalent to atoms, so that rotational transitions are neglected. Oxygen does not give satisfactory results with this model, possibly owing to the rôle of non-van der Waals forces in the crystals. F. A. Lindemann's semi-empirical correlation between the melting point and the Einstein frequency of the crystals is also derived from the theory. The possibility of a continuous transition between solid and liquid above a critical pressure and temperature [46] has also been discussed, in view of its importance for geophysical theories.

With the present experimental evidence, the particular type of lattice disorder assumed by Lennard-Jones may be regarded as convenient for calculation, without necessarily excluding other types of lattice defects. From the behaviour of solid solutions, there is some experimental evidence for co-operative defects, in which the energy of β sites is lowered when these occur in a suitable relationship.[26]

Theories of melting in which the emphasis is laid on the change in mechanical properties, associated with the phase change, have

[45] J. E. Lennard-Jones and A. F. Devonshire, *Proc. Roy. Soc.*, 1939, **169**, *A*, 317; **170**, *A*, 464; A. F. Devonshire, *ibid.*, 1940, **174**, *A*, 102; J. E. Lennard-Jones, *Proc. Physical Soc.*, 1940, **52**, 38.

[46] P. W. Bridgman, *Physical Rev.*, 1934, **46**, 930; *Proc. Amer. Acad. Arts Sci.*, 1935, **70**, 1.

not been worked out in the same detail.[47]   One of the obstacles
is the want of a completely satisfactory theory of the mechanical
properties of crystals, in relation to their structure.[48]   Attention
may be drawn to a semi-empirical approach [49] based on Sutherland's
empirical formula for the rigidity modulus μ : [50]

$$\mu = \mu_0[1 - (T/T_m)^2]$$

The radiation pressure due to standing waves in the crystal, *i.e.*, to
the thermal oscillations, can be expressed in terms of this rigidity
modulus and the temperature, and automatically leads to a phase
with no macroscopic rigidity above the melting point.   For very
small crystals, however, which only contain standing waves of high
frequency, the microscopic rigidity modulus may remain finite at
the melting point.[51]   Hence very small crystals may persist to
somewhat higher temperatures.   Although these views are not
yet well defined, they contain a number of features which any
mechanical theory of melting must take into account.

Finally, brief mention may be made of the topic of premelting.
No experimental means has yet been devised which decides whether
the transition from solid to liquid really occurs at a single temper-
ature, or over a more or less narrow but finite interval, depending
on the crystal structure.[26]   Actual measurements of the volume
change or heat change have always shown a transition over a
narrow range of temperatures : for instance, for very pure mercury
a volume change was observed extending over an interval of $0 \cdot 024°$.[52]
This behaviour has hitherto been explained on the assumption of
impurities insoluble in the solid phase, but there is little theoretical
difficulty in modifying the thermodynamic equations for a phase
transition to account for transitions over a narrow temperature
interval, instead of a melting point.[53]   One view is that the
fluctuations may be unusually large near the melting point,[54] so
that it would be difficult to define the temperature with any
accuracy—say, to $10^{-4°}$.

Though the significance of premelting must be regarded as un-
decided at present, the topic is of some interest in view of its con-
nection with the abnormally low mechanical strength of crystals.[13]

[47] M. Born, *Nature*, 1940, **145**, 741; *J. Chem. Physics*, 1939, **7**, 591;
R. Furth, *Nature*, 1940, **145**, 742.
[48] Cf. discussion in *Proc. Physical Soc.*, 1940.
[49] R. Lucas, *Compt. rend.*, 1938, **207**, 1408.
[50] W. Sutherland, *Phil. Mag.*, 1891, [v], **32**, 31, 215, 524.
[51] L. Brillouin, *Physical Rev.*, 1938, **54**, 916.
[52] A. Smits and G. J. Muller, *Z. physikal. Chem.*, 1937, **36**, B, 288.
[53] A. Rutgers and S. Wouthuysen, *Physica*, 1937, **4**, 235, 515.
[54] J. Frenkel, *J. Chem. Physics*, 1939, **7**, 538; E. Brody, *ibid.*, p. 538.

Transition from the Crystalline to Special States of Matter.—In addition to the transition from the crystalline to the anisotropic liquid state, a number of related transitions are known, which throw further light on the modes of entropy increase in crystals. The most familiar of these is the transition to the liquid crystal state. Since the previous report on liquid crystals,[55] work has been rather spasmodic. References to recent discussions include those given below,[56] but a fuller discussion must be left for a subsequent report.

A large amount of work has recently been published on the transition from the crystalline to the rubber-like state of matter.[57] In addition to natural rubber, a number of polymerised hydrocarbons have been discovered, which normally exist in what is best described as a new state of matter. Two main properties of the rubber state, which throw light on its statistical make-up, are its behaviour on cooling and on stretching. X-Ray photographs of unstretched rubber at ordinary temperatures show only diffuse rings, comparable to those of a liquid or a gas. When the rubber is cooled to a fairly low temperature, the photographs change to the sharp rings given by a polycrystalline material, so that in this respect rubber resembles the more familiar liquids. As was first discovered by J. R. Katz,[58] when rubber is stretched at room temperature, X-ray photographs show that crystallisation likewise takes place. It has long been known that heat is evolved on stretching rubber. The thermodynamic consequence, that Young's modulus for rubber has a positive temperature coefficient, over a range of temperature, is in contrast with the majority of crystalline solids. The liberation of heat and the crystallisation which occur on stretching show that the entropy of the molecules is decreased in the process.

[55] *Ann. Reports*, 1931, **28**, 280.

[56] F. C. Frank and K. Wirtz, *Naturwiss.*, 1938, **26**, 688, 697; L. Ornstein, *Proc. K. Akad. Wetensch. Amsterdam*, 1938, **41**, 1046; R. Furth and K. Sitte, *Ann. Physik*, 1937, [v], **30**, 388; W. Kast, *Z. Elektrochem.*, 1939, **45**, 184; C. Weygand and R. Gabler, *Z. physikal. Chem.*, 1939, **44**, *B*, 69; D. Vorlander, *Z. Krist.*, 1931, **79**, 61; *Ber.*, 1938, **71**, 1688.

[57] *E.g.*, E. Guth and H. Mark, *Z. Elektrochem.*, 1937, **43**, 683; F. Dart and E. Guth, *Physical Rev.*, 1938, **53**, 327; H. Mark, *Nature*, 1938, **141**, 670; *Z. physikal. Chem.*, 1938, **38**, *B*, 395; F. Misch and A. van der Wyk, *J. Chem. Physics*, 1940, **8**, 127; *Helv. Chim. Acta*, 1939, **22**, 1358, 1362; W. Smith and C. Saylor, *J. Res. Nat. Bur. Stand.*, 1938, **21**, 257; G. Clark, *ibid.*, **22**, 105; S. Bresler and J. Frenkel, *Acta Physicochim. U.R.S.S.*, 1939, **11**, 485; J. Frenkel, *ibid.*, 1938, **9**, 235; W. Kuhn, *Z. Elektrochem.*, 1939, **45**, 335; E. Wohlisch, *Kolloid-Z.*, 1939, **89**, 239; *Z. physikal. Chem.*, 1939, **184**, 416; E. Sauter, *ibid.*, 1937, **36**, *B*, 405; P. Thiessen and W. Kirsch, *ibid.*, 1939, **43**, *B*, 292; 1938, **41**, *B*, 33.

[58] *Kolloid-Z.*, 1925, **36**, 300; **37**, 19.

These and other facts about the transition from the crystalline to the rubber state have been interpreted by assuming that the very long hydrocarbon molecules can increase their entropy by coiling up, through rotations about the C–C bonds. The large number of possible states of coiling results in a considerable increase in entropy, as a result of the transition, and this explains why the equilibrium state of unstretched rubber has the majority of the molecules in the coiled state, even at room temperature.

Details of the statistical treatment will be found in the original papers. Although not all the possible states of the molecules are known in such a complex mixture of polymers as rubber, this type of change of state has its importance, even outside rubber chemistry. Other complex organic molecules, such as the proteins, may have modes of entropy increase, connected with changes of " crystal structure " in the wider sense, which are intimately connected with such problems as the thermodynamics of muscular work.   A. R. U.

3. HINDERED ROTATION ABOUT SINGLE BONDS.

Where it is applicable, X-ray crystal analysis is the method capable of furnishing most detailed information regarding molecular structure. Evidence as to how far crystal forces may alter the configuration of a molecule is therefore of some interest.

Great importance consequently attaches to the recent discovery of high-energy barriers hindering so-called " free rotation " about single covalency bonds, even in quite simple compounds. For example in molecules such as s-dichloroethane in the gaseous state evidence from electron-diffraction [1] and from dipole moments [2] indicates that rotation about the C–C bond is hindered by a potential barrier almost certainly higher than 4 kg.-cals./mol. More remarkable is the suggestion, first made by J. D. Kemp and K. S. Pitzer,[3] and subsequently confirmed by many others,[4] that even in ethane and its homologues the hindering potential is of the order of 3 kg.-cals./mol. This hypothesis is based mainly upon a comparison of the observed entropy (or heat capacity—a related quantity) of the gas with those calculated by statistical mechanics on the basis of

[1] This vol., p. 64; J. Y. Beach and K. J. Palmer, *J. Chem. Physics*, 1938, **6,** 639.

[2] *E.g.,* J. Y. Beach and D. P. Stevenson, *ibid.,* p. 635; this vol., p. 59.

[3] *Ibid.,* 1936, **4,** 749; *J. Amer. Chem. Soc.,* 1937, **59,** 276.

[4] G. B. Kistiakowsky and F. Nazmi, *J. Chem. Physics*, 1938, **6,** 18; K. Schäfer, *Z. physikal. Chem.,* 1938, **40,** *B,* 357; E. B. Wilson, junr., *J. Chem. Physics,* 1938, **6,** 740; G. B. Kistiakowsky, J. R. Lacher, and F. Stitt, *ibid.,* 1939, **7,** 289.

molecular models corresponding to various barriers; but it is supported by other data.[5]   Barriers of the same order of magnitude have been detected in many other simple molecules.[6]   Steric effects, calculated in a manner suggested by H. Eyring,[7] are possibly adequate to account for the barriers observed in substituted ethanes (e.g., $CH_2Cl \cdot CH_2Cl$ [8]), but not for that in ethane itself; and here the only explanations so far put forward [9] would require the stable configuration to be the " opposed," or " eclipsed " (of symmetry D_{3h}), rather than the " staggered " one (D_{3d}), which on general grounds is regarded as much the more probable.[10]

These high barriers to internal rotation, being considerably larger than the estimated threshold energies for the rotation of the molecule as a whole in the crystal,[11] will oppose the assumption by the molecule of any configuration different from the mean configuration occurring in the gas.   Certainly with small compact molecules, therefore, rotation of the molecule as a whole will take place rather than any considerable permanent distortion of its parts.   As an example, K. S. Pitzer [12] concludes from a study of the thermal properties of solid s-dichloro- and -dibromo-ethane that, although total molecular rotation occurs when the temperature is sufficiently high, there is no internal rotation about the C–C bond in the crystal; and R. W. Sillars [13] and D. R. Pelmore [14] conclude that the dielectric behaviour of solutions in solid waxes of certain long-chain esters indicates that the ester molecules rotate rigidly.   On the other hand, with long polymethylene chains an accumulation of small oscillations

[5] E.g., J. B. Howard, J. Chem. Physics, 1937, 5, 451; B. L. Crawford, junr., W. H. Avery, and J. W. Linnett, ibid., 1938, 6, 682.

[6] J. G. Aston, Chem. Reviews, 1940, 27, 63 (for other references); C. R. Bailey, S. C. Carson, and E. F. Daly, Proc. Roy. Soc., 1940, 173, A, 347; G. B. Kistiakowsky and W. W. Rice, J. Chem. Physics, 1940, 8, 610;   J. S. Koehler and D. M. Dennison, Physical Rev., 1940, 57, 1006;   D. W. Osborne, R. N. Doescher, and D. M. Yost, J. Chem. Physics, 1940, 8, 506; L. R. Zumwalt and R. M. Badger, J. Amer. Chem. Soc., 1940, 62, 305; J. G. Aston and A. M. Kennedy, ibid., p. 2567; B. L. Crawford, jun., J. Chem. Physics., 1940, 8, 744.

[7] J. Amer. Chem. Soc., 1932, 54, 3191.

[8] J. Y. Beach and K. J. Palmer, J. Chem. Physics, 1938, 6, 642.

[9] E. Gorin, J. Walter, and H. Eyring, J. Amer. Chem. Soc., 1939, 61, 1876; A. Eucken and K. Schäfer, Naturwiss., 1939, 27, 122.

[10] B. L. Crawford, junr., W. H. Avery, and J. W. Linnett, J. Chem. Physics, 1938, 6, 682; J. B. Conn, G. B. Kistiakowsky, and E. A. Smith, J. Amer. Chem. Soc., 1939, 61, 1872; K. S. Pitzer, Chem. Reviews, 1940, 27, 44; V. Schomaker and D. P. Stevenson, J. Chem. Physics, 1940, 8, 637.

[11] E.g., L. Pauling, Physical Rev., 1930, 36, 430; Alex Müller, Helv. Physica Acta, 1936, 9, 626;   J. G. Kirkwood, J. Chem. Physics, 1940, 8, 205.

[12] J. Amer. Chem. Soc., 1940, 62, 331; see also A. H. White and W. S. Bishop, ibid., p. 16.

[13] Proc. Roy. Soc., 1938, 169, A, 66.   [14] Ibid., 1939, 172, A, 502.

about each C–C bond may give rise to a considerable torsional flexibility between the ends of the chain.[15]   J. M. Robertson and his collaborators [16] have found that crystals of stilbene and of *trans*-azobenzene contain two kinds of molecule, differing with respect to the orientations of the two benzene rings; but the difference in orientation is very small—about 15°.   (It may be noted that, if the opposed were the stable configuration in ethane and its homologues, then the flat zigzag · shape normally assumed by polymethylene chains in crystals or in monolayers—a shape requiring the staggered configuration round each C–C bond—could not be formed without great strain.)

In some other instances, where crystal analysis has shown groups to be greatly distorted from their normal orientations, the distortion can be attributed to large steric effects, which would presumably operate similarly were the molecules in the gaseous state.   This applies to the conclusion of C. J. B. Clews and K. Lonsdale [17] that in solid *o*-diphenylbenzene the phenyls are twisted through some 50° from the plane of the C_6H_4 nucleus; to that of J. M. Robertson [17a] that in solid *cis*-azobenzene the rings are also twisted through some 50° from the plane of the central C–N=N–C atoms [a displacement no doubt contributing towards the (algebraically) lower energy of formation of the *cis*-isomer [18]]; to that of G. Huse and H. M. Powell [19] that the *o*-nitro-groups in picryl iodide are rotated through 80° from the plane of the ring; and to that of J. D. McCullough [20] (obtained by an interesting extension of the radial distribution method to X-ray powder photographs) that, whilst *meso*-stilbene dibromide has a *trans*-configuration, the molecule in the racemic form is twisted by 90° (in which direction is not certain) from that configuration in which the two bromine atoms are *trans* to one another.

A somewhat different aspect of the case is implied in the work of S. Mizushima, Y. Morino, and their collaborators,[21] and of L. Kahovec and K. W. F. Kohlrausch,[22] who show that a number of frequencies present in the Raman spectra of liquid or dissolved ethylene di-

[15] This vol., p. 172.

[16] J. M. Robertson and (Miss) I. Woodward, *Proc. Roy. Soc.*, 1937, **162**, *A*, 568; J. J. de Lange, J. M. Robertson, and (Miss) I. Woodward, *ibid.*, 1939, **171**, *A*, 398.

[17] *Proc. Roy. Soc.*, 1937, *A*, **161**, 493; see also K. Lonsdale, *Z. Krist.*, 1937, **97**, 91.

[17a] *J.*, 1939, 232.

[18] R. J. Corruccini and E. C. Gilbert, *J. Amer. Chem. Soc.*, 1939, **61**, 2925.

[19] *J.*, 1940, 1398.   [20] *J. Amer. Chem. Soc.*, 1940, **62**, 480.

[21] *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1936, **29**, 63; 1939, **36**, 281; 1940, **37**, 205.

[22] *Ber.*, 1940, **73**, 159.

halides and related compounds are absent from the spectra of the corresponding solids. Broadly speaking, both groups of workers agree in attributing this to a restriction of the molecules in the crystal to a single configuration (in the dihalides, for instance, *trans*) ; in the " mobile " states the restriction is relaxed, so that another form may exist also (in the dihalides probably a *cis*-form). As mentioned above [1, 2] the evidence leads to the conclusion that there is no appreciable proportion of *cis*-molecules present in the vapours of these dihalides. The work of E. Fischer [23] on dielectric properties makes it appear possible that the rotation of groups may be more nearly free in the liquid than in the gaseous or the solid state, though there is evidence that barriers to internal rotation do occur in dissolved molecules.[24]   J. C. S.

4. INORGANIC STRUCTURES.

Inevitably the number of structure determinations which have been carried out during the past year is less than in previous years, and as no obvious general problem has been pursued, a brief mention only will be made in the second sub-section of this report of some of the more interesting individual cases. Two papers, however, on the general problem of directed valency have recently appeared and are of considerable interest. In the first of these [1] the problem has been treated from the group-theory point of view; it is really an extension of the earlier work of Pauling and Mulliken,[2] and in it are discussed the spatial arrangements of all possible electron configurations from two to eight s, p, or d valency electrons on a central atom. The method does not predict directly the type of bond arrangement formed by any given electron configuration, but merely tells whether or not a given arrangement is possible. In some cases it is found that several arrangements are possible for a single configuration of electrons; for example, where we have a central atom covalently linked to two other atoms in a molecule AX_2, the electron configurations sp and dp can lead to either a linear or an angular arrangement; the configurations ds, d^2, and p^2, on the other hand, must be angular. In those cases where there is ambiguity, the arrangement which is adopted can only be predicted by applying other criteria to determine the relative stability of the various arrangements. Such criteria might be the " strength " of the bonds as determined by

[23] *E.g.*, *Physikal. Z.*, 1939, **40**, 645; see also T. Y. Wu, *J. Chem. Physics*, 1939, **7**, 967.

[24] *E.g.*, G. L. Lewis and C. P. Smyth, *ibid.*, p. 1085.

[1] G. E. Kimball, *J. Chem. Physics*, 1940, **8**, 188.

[2] L. Pauling, *J. Amer. Chem. Soc.*, 1931, **53**, 1367; R. S. Mulliken, *J. Chem. Physics*, 1933, **1**, 492.

the degree of overlapping of the bond orbitals,[3] or considerations of repulsion between non-bonded atoms, or the possibility of utilising orbitals for the formation of "resonating" double bonds. In mercuric chloride, for example, where the electron configuration is sp, a linear rather than an angular arrangement is favoured both because of the repulsive forces and also because of the possibility of resonance with $Cl\rightleftharpoons Hg\rightleftharpoons Cl$. It must be emphasised that group theory cannot tell us anything about the relative stabilities of the various electron configurations, any more than it can tell us of the likelihood of occurrence of any of the 230 space groups; if, however, an atom is known to have a certain electron configuration, its possible spatial arrangements can be deduced.

It is because of the difficulty which many chemists experience of knowing what electron configurations are involved in bond formation, that N. V. Sidgwick and H. M. Powell [4] have collected together the experimental evidence, and correlated the stereochemistry of a multivalent atom with the size of its valency group and the number of shared electrons which it contains, together with the number of electrons (unshared) in the penultimate electronic group. X-Ray and electron-diffraction experiments have shown that stereochemical configurations tend to conform to quite a limited number of types, and the conditions under which they are formed can be stated as follows :

I. When the valency group is less than an octet, the electrons take up positions of highest symmetry, namely, a linear arrangement for a group of 4, as in mercuric chloride, and plane symmetrical for a group of 6, as in boron trifluoride. This also appears to be the arrangement when the sextet is not fully shared, as in covalent stannous chloride and lead bromide.

II. With a complete octet the arrangement can be either tetrahedral or planar. When the covalency is less than 4 it is always derived from the tetrahedron as in the triangular water and the pyramidal ammonia.* The fully shared octet is always tetrahedral

* A linear arrangement, however, with a bicovalent octet has been observed in certain crystal structures, e.g., the P–O–P group in the pyrophosphate ion $[P_2O_7]^{-4}$,[5] and the S–S–S group in the trithionate ion $[S_3O_6]^{-2}$.[6] This may be due to the contribution of structures such as

$$\overset{}{O}-\overset{\overset{O}{\|}}{\underset{\underset{O}{|}}{P}}\overset{++}{=}\overset{}{O}\overset{++}{=}\overset{\overset{O}{\|}}{\underset{\underset{O}{|}}{P}}-\overset{}{O}.$$

[3] L. Pauling, " The Nature of the Chemical Bond," p. 76.

[4] Bakerian Lecture, *Proc. Roy. Soc.*, 1940, **176,** *A*, 153.

[5] G. R. Levi and G. Peyronel, *Z. Krist.*, 1935, **92,** 190; G. Peyronel, *ibid.*, 1936, **94,** 511.

[6] W. H. Zachariasen, *ibid.*, 1934, **89,** 529.

when the penultimate group is completed (2, 8, or 18 electrons).* In the transitional elements where the number in the penultimate group lies between 8 and 18, the arrangement is tetrahedral when the penultimate group contains not much more than 8, and planar when it contains not much less than 18 electrons, the two series overlapping in the middle. The square planar arrangement may be regarded as that of an octahedron with the two *trans*-positions unoccupied, and Sidgwick and Powell have suggested that it may involve a 4-covalent duodecet 4, *8*, as we have in the planar $[ICl_4]^-$ ion.† If this is so, the electronic configuration should be written, not as (n), 8, but as $(n-4)$, 4, *8*, and since the penultimate group cannot be reduced below 8, the planar structure would only become possible when n is at least 12, which is roughly where it first appears.

III. With a valency group of 10 electrons, whether they are fully shared or not, the arrangement would always appear to be that derived from a trigonal bipyramid. Thus when only 4 are shared as in the ions $[ICl_2]^-$, $[I_3]^-$, etc., which are known to be linear,[8] the configuration can be considered that of a trigonal bipyramid with halogen atoms at the two pyramidal apices and the three unshared electron pairs in the equatorial plane. The structure of the covalent iodochlorides $ArICl_2$, where six of the ten electrons are shared, has not been examined, but from the foregoing one would expect a planar arrangement with the two unshared electron pairs now at the pyramidal apices.

Two interesting structures involving a decet with eight shared electrons have recently been determined, the crystal structure of potassium fluoroiodate, KIO_2F_2, being investigated by means of X-rays [9] and the structure of tellurium tetrachloride in the vapour phase by the method of electron diffraction.[10] In the former the $[IO_2F_2]^-$ ion is composed of an iodine atom forming bonds at approximately 100° with two oxygen atoms, and, perpendicular to the plane of these three atoms, two opposed bonds at 180° to the two fluorine atoms; the third position in the IO_2 equatorial plane of the trigonal bipyramid is presumably occupied by the unshared pair. A similar (somewhat distorted) trigonal bipyramidal configuration has been

[7] H. J. Dothie, F. J. Llewellyn, W. Wardlaw, and A. J. E. Welch, *J.*, 1939, 426.

[8] R. W. G. Wyckoff, *J. Amer. Chem. Soc.*, 1920, **42,** 1100; R. C. L. Mooney, *Z. Krist.*, 1935, **90,** 143; 1938, **98,** 324; 1939, **100,** 519.

[9] L. Helmholz and M. T. Rogers, *J. Amer. Chem. Soc.*, 1940, **62,** 1537.

[10] D. P. Stevenson and V. Schomaker, *ibid.*, p. 1267.

* A possible exception is $K[Au(CN)_2dipy]$ which appears to be planar [7] although the gold atom has the structure (18) *8*.

† It is noteworthy that atoms such as Pd and Pt which can exhibit both square and octahedral co-ordination have the same covalent radii in both these forms.

proposed for the tellurium halide as being in best accord with the electron-diffraction measurements, the unshared pair again occupying one of the equatorial positions.* The configuration is presumably that due to (incomplete) sp^3d hybridisation, and not to p^3d with the unshared pair occupying a pure s orbital as was assumed by Kimball,[1] since this would lead to an irregular tetrahedral configuration of symmetry C_{3v}.

There are, however, a number of cases known where there is apparently a valency group of ten of which eight are shared, which do not conform to this stereochemical type derived from a trigonal bipyramid. These include the 4-covalent complexes of univalent thallium, such as $[Tl\{SC(NH_2)_2\}_4]NO_3$, and of bivalent lead, such as $K_2[Pb(C_2O_4)_2]$. The structures of these compounds have not been investigated in detail but enough has been done to establish their planar character.[12] It is by no means certain, however, that these cases involve a decet at all. If we consider the complex plumbous oxalate, the usual way of writing this ion is (I), giving the metal the electron configuration (78), 2, 8 and a formal charge of -2, which is surprising when we remember that lead is an electropositive element.

(I.)   (II.)
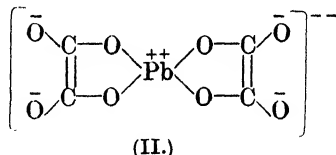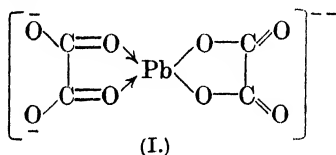
An alternative structure would be (II), in which the lead has the electronic configuration (76), 8. The inner 76 electrons can then be placed in the orbitals $1s2s2p^33s3p^33d^54s4p^34d^54f^75s5p^35d^4$ leaving the fifth $5d$ orbital as well as the $6s$ and $6p$ orbitals available for bond formation. The 8 shared electrons would then occupy these orbitals to give square $5d6s6p^2$ bonds.

A number of cases have been examined of compounds containing a fully shared decet (*e.g.*, phosphorus pentafluoride) and they have all been shown to be of the trigonal bipyramid type; further recent examples include niobium and tantalum chlorides and bromides.[13] It is noteworthy that this is the arrangement which has been found in all 5-covalent compounds, even with an incomplete penultimate group as in $MoCl_5$ and $Fe(CO)_5$. It is unfortunate that, owing to

* This is also in agreement with the large dipole moment of 2·54 D. found for $TeCl_4$ in benzene solution.[11]

[11] C. P. Smyth, A. J. Grossman, and S. R. Ginsburg, *J. Amer. Chem. Soc.*, 1940, **62**, 192.

[12] E. G. Cox, A. J. Shorter, and W. Wardlaw, *Nature*, 1937, **139**, 71; *J.*, 1938, 1886.

[13] H. A. Skinner and L. E. Sutton, *Trans. Faraday Soc.*, 1940, **36**, 668.

the large difference between the atomic numbers of the atoms, the spatial configuration of iodine pentafluoride has not been determined. Here the iodine has 12 valency electrons of which 10 are shared, and, by analogy with $[IF_4]^-$, one might expect a square pyramid structure (*i.e.*, an octahedron with one of the corners occupied by the unshared pair).

IV. With a covalency of six we should expect three possible arrangements : (*a*) a trigonal prism, (*b*) a trigonal antiprism, (*c*) a regular octahedron ; (*c*) is simply a special case of (*b*) in which all the edges and angles are equal. Octahedral bonds are formed by the configuration d^2sp^3 and no other,[14] and hence Kimball argues that the commonness of this arrangement is due to the fact that the configuration d^2sp^3 is the usual configuration of six valency electrons rather than to any particular virtue of the octahedral arrangement. Sidgwick and Powell, on the other hand, consider that the octahedron is to be preferred for geometrical reasons, since it is in this arrangement that the strain due to repulsion between non-bonded atoms is a minimum. Certainly, octahedral bonds have been observed in practically every type of complex AB_6, it being only in giant molecules of the molybdenum disulphide and nickel arsenide type, where the complexes are subject to strong valency forces, that the trigonal prismatic form occurs.[15]

It should be pointed out, however, that the octahedral d^2sp^3 configuration can arise in more than one way. With the large class of 6-co-ordinated ions of the transition elements, it is the d orbitals of the penultimate group, having about the same energy as the s and p orbitals of the valency group, which take part in bond formation ; *e.g.*, with $[Fe(CN)_6]^{-4}$ the hybridisation is $3d^24s4p^3$, with $[PtCl_6]^{-2}$ it is $5d^26s6p^3$. In those cases, however, either where there are no d orbitals in the penultimate group (*e.g.*, sulphur hexafluoride), or where these orbitals are fully occupied by unshared electron pairs, *e.g.*, $[SnCl_6]^{-2}$, use must be made of the unstable d orbitals of the valency shell itself, the hybridisation in the case of the hexafluoride being $3s3p^33d^2$, and in the case of the chlorostannate ion $5s5p^35d^2$. Still another case is where we have the phenomenon of the " inert pair," as in $[SeBr_6]^{-2}$. Here the fourteen electrons (12 shared + the inert pair) might occupy the orbitals 4s, three 4p, and three 4d, and if, as might be supposed, the unshared pair occupied the orbital of greatest coulombic stability, *viz.*, the 4s, the configuration of the bonds would be $4p^34d^3$, giving an antiprismatic arrangement. The arrangement, however, is observed to be octahedral, and hence Kimball suggests that the unshared pair occupies a 4d rather than

[14] G. E. Kimball, *loc. cit.*, ref. (1).
[15] R. Hultgren, *Physical Rev.*, 1932, **40**, 891.

the $4s$ orbital, leaving the bond configuration $4s4p^34d^2$. A more likely explanation [16] is that the inert pair does occupy the stable $4s$ orbital and that the $5s$ orbital is utilised in bond formation, the configuration being $4p^34d^25s$; this view is in agreement with the large octahedral radius of selenium observed in these complexes.

V. A covalency of 7 is extremely rare, but two different types have been observed; [17] the $[ZrF_7]^{-3}$ structure which may be derived from an octahedron by adding a fluorine atom at the centre of one face, and the $[NbF_7]^{-2}$ or $[TaF_7]^{-2}$ structure which may be obtained from a trigonal prism by adding a fluorine atom at the centre of a prism face. The central atoms in these complexes are isoelectronic, and there is no obvious explanation for this surprising difference in stereochemical arrangement.

VI. Only one 8-covalent complex has been examined, namely, $[Mo(CN)_8]^{-4}$, and it has been shown that the arrangement is that of a dodecahedron.[18] The configuration therefore, according to Kimball, is d^4sp^3, the dodecahedron being more stable than either the cubic or the antiprismatic structure. For the ion $[TaF_8]^{-3}$ and the molecule OsF_8 with the configuration d^5sp^2, Kimball predicts a face-centred prismatic structure.

Recent Structures.

Metallic holmium has a hexagonal closest-packed structure, with six nearest neighbours at a distance of 3·48 A. and six at 3·557 A.[19] Of the oxides, the high-temperature form of potassium hydroxide has a rock-salt structure, the radius of the OH^- ion being 1·53 A.[20] The sesquioxides of rubidium and caesium, Rb_2O_3 and Cs_2O_3, do not contain the ion O_3^{--}, but should be formulated as $Rb_2O_2.2RbO_2$, the magnetic susceptibilities being consistent with a proportion of one peroxide ion $^-:\overset{..}{O}-\overset{..}{O}:^-$ to two superoxide ions : $\overset{..}{O}\dot{=}\overset{..}{O}:$, the latter having a three-electron bond.[21] A study of the uranium–sulphur system has revealed the existence of a subsulphide U_4S_3 having a sodium chloride structure in which one-quarter of the anion positions are left vacant;[22] and the subphosphides of iridium and rhodium, Ir_2P and Rh_2P, are of the anti-calcium fluoride type with the distances Ir–P$=$2·40 A. and Rh–P $=$ 2·38 A. An interesting structure which has been worked out completely by Patterson and Fourier analysis

[16] J. Y. Beach, quoted by L. Pauling, *op. cit.*, p. 171.

[17] See *Ann. Reports*, 1939, **36**, 168, 170.

[18] J. L. Hoard and H. H. Nordsieck, *J. Amer. Chem. Soc.*, 1939, **61**, 2853.

[19] H. Bommer, *Z. anorg. Chem.*, 1939, **242**, 277.

[20] W. Teichert and W. Klemm, *ibid.*, **243**, 138.

[21] A. Helms and W. Klemm, *ibid.*, **242**, 201; L. Pauling, *op. cit.*, p. 252.

[22] E. F. Strotzer, O. Schneider, and W. Biltz, *Z. anorg. Chem.*, 1940, **243**, 307; M. Zumbusch, *ibid.*, p. 322.

is that of tetraphosphonitrile chloride, $P_4N_4Cl_8$.[23] The molecule consists of a puckered 8-membered ring of alternate nitrogen and phosphorus atoms, each phosphorus carrying two chlorine atoms and having approximately a tetrahedral arrangement of its four linkages. The angles within the ring are roughly 122° for nitrogen and 117° for phosphorus and the P–N distances are all approximately 1·67 A. Since the distance calculated for a single bond is 1·80 A. and for a double bond 1·61 A., the eight-membered ring appears to possess an " aromatic " structure of resonating single and double bonds. Although phosphorus pentachloride has been shown by electron diffraction to have a trigonal bipyramidal configuration in the vapour phase, the crystal structure of this substance and also that of the bromide are entirely different. Crystalline phosphorus penta-chloride is ionic, being composed of tetrahedral $[PCl_4]^+$ ions and octa-hedral $[PCl_6]^-$ ions,[24] whilst crystalline phosphorus pentabromide is built up of tetrahedral $[PBr_4]^+$ ions and Br^- ions, the latter being twice as far removed from the phosphorus as the four covalently linked atoms.[25] The difference between the two crystalline struc-tures may be due to the instability of an octahedral $[PBr_6]^-$ complex, arising from the larger size of the bromine atoms. In a metastable modification of anhydrous sodium sulphate, Na_2SO_4-III, an S–O distance of $1·52 \pm 0·03$ a. in the SO_4^{--} ion has been reported [26]; on the other hand, a careful examination of potassium sulphamate, $NH_2 \cdot SO_3K$, has given the values $S–O = 1·44 \pm 0·03$ a. and $S–N = 1·57 \pm 0·03$ a. for the tetrahedral $NH_2 \cdot SO_3^-$ ion.[27] The explanation for the shorter S–O distance may be that the sulphamate ion has only a single negative charge whereas the sulphate ion is doubly charged. These distances are even shorter than those to be expected for double bonds.

In sodium formate there is complete resonance between the two C–O bonds of the formate ion, the bond angle of 124° and C–O dis-tance of 1·27 a. agreeing with those (125° and 1·29 a.) found in formic acid dimer by electron diffraction.[28] A redetermination of the parameters in NH_4HF_2 [29] has given an F---H---F distance of $2·32 \pm 0·03$ a. This is greater than that ($2·26 \pm 0·01$ a.) found in KHF_2,[30]

[23] J. A. A. Ketelaar and T. A. de Vries, *Rec. Trav. chim.*, 1939, **58**, 1081.

[24] H. M. Powell, D. Clark, and A. F. Wells, *Nature*, 1940, **145**, 149.

[25] H. M. Powell and D. Clark, *ibid.*, p. 971.

[26] L. K. Frevel, *J. Chem. Physics*, 1940, **8**, 290.

[27] C. J. Brown and E. G. Cox, *J.*, 1940, 1.

[28] W. H. Zachariasen, *J. Amer. Chem. Soc.*, 1940, **62**, 1011; L. Pauling and L. O. Brockway, *Proc. Nat. Acad. Sci.*, 1934, **20**, 340.

[29] M. T. Rogers and L. Helmholz, *J. Amer. Chem. Soc.*, 1940, **62**, 1533.

[30] L. Helmholz and M. T. Rogers, *ibid.*, 1939, **61**, 2590; *Ann. Reports*, 1939, **36**, 165.

showing that in the ammonium compound the bonds are weakened by the formation of the two additional hydrogen bonds $H_3N-H\cdots F\cdots H\cdots F\cdots H-NH_3$.

A series of hexafluogermanates, M_2GeF_6, which have been examined [31] show an interesting change of structure according as $M = NH_4$, K, Rb, or Cs. As is to be expected, the GeF_6^{--} ion has an octahedral configuration with Ge–F $= 1\cdot77$ A., but the packing of the GeF_6^{--} ions and the alkali ions changes through the series. The ammonium and the potassium salt are isomorphous, the structures corresponding very approximately to hexagonal closest packing of alkali and fluorine atoms, as in the low-temperature modification of ammonium silicofluoride;[32] each cation is surrounded by nine nearly equidistant fluorine atoms and three others at a somewhat greater distance. With the rubidium salt the structure is still hexagonal, but here the Rb^+ ions appear to have twelve equidistant fluorine neighbours. The cæsium salt, on the other hand,[33] has the well-known cubic structure of the ammonium chloroplatinate type, the co-ordination number of the cations again being twelve. This same structure has also been observed for cæsium hexachlorogermanate Cs_2GeCl_6.[34]

In an extensive investigation of the complexes formed between tertiary phosphines and arsines and the halides of cadmium and mercury,[35] five different classes of compound have been isolated. These can be represented as (a) $(R_3P)_2MX_2$, (b) $(R_3P)_2(MX_2)_2$, (c) $(R_3P)_2(MX_2)_3$, (d) $(R_3P)_2(MX_2)_4$, and (e) $(R_3P)_3(MX_2)_2$, mercuric halides forming complexes of all five types whilst cadmium halides form only complexes of types (a), (b), and (e). In most cases only a preliminary structure determination has been carried out, but it is considered that complexes of the type (a) probably consist of discrete molecules having a tetrahedral arrangement [cf., on the other hand, the structures of $(NH_3)_2CdX_2$ and $(NH_3)_2HgX_2$].[36] Complexes of the type (b) are centrosymmetric and presumably have the trans-bridged structure (III) similar to the 4-covalent dipalladium [37] and diauric [38] complexes, except that in the cases of the cadmium and
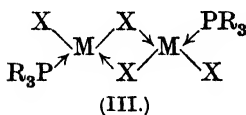
(III.)

[31] J. L. Hoard and W. B. Vincent, J. Amer. Chem. Soc., 1939, **61**, 2849.

[32] B. Gossner and O. Kraus, Z. Krist., 1934, **88**, 223.

[33] R. W. G. Wyckoff and J. H. Müller, Amer. J. Sci., 1927, **13**, 347.

[34] A. W. Laubengayer, O. B. Billings, and A. E. Newkirk, J. Amer. Chem. Soc., 1940, **62**, 546.

[35] R. C. Evans, F. G. Mann, H. S. Peiser, and D. Purdie, J., 1940, 1209.

[36] C. H. MacGillavry and J. M. Bijvoet, Z. Krist., 1936, **94**, 231, 249.

[37] F. G. Mann and co-workers, J., 1938, 702, 1949, 2086; 1939, 1622.

[38] A. Burawoy, C. S. Gibson, G. C. Hampson, and H. M. Powell, J., 1937, 1690.

mercuric complexes, X-ray evidence indicates a tetrahedral rather than a planar configuration. With complexes of the type (c) (given only by mercury) there appear to be two distinct possibilities. $(Bu_3As)_2(HgBr_2)_3$, whose structure has been worked out in some detail, is essentially a molecular compound of $(Bu_3As)_2(HgBr_2)_2$ [the same as type (b)] and $HgBr_2$, as shown in the figure, where the

2·25   2·25

3·1   3·2

2·25   135°
2·6
93°   87°
2·9

2·25
87°   93°
135°   2·9
2·25   2·6

3·2   3·1

2·25   2·25

○ Hg   ◎ As   ○ Br
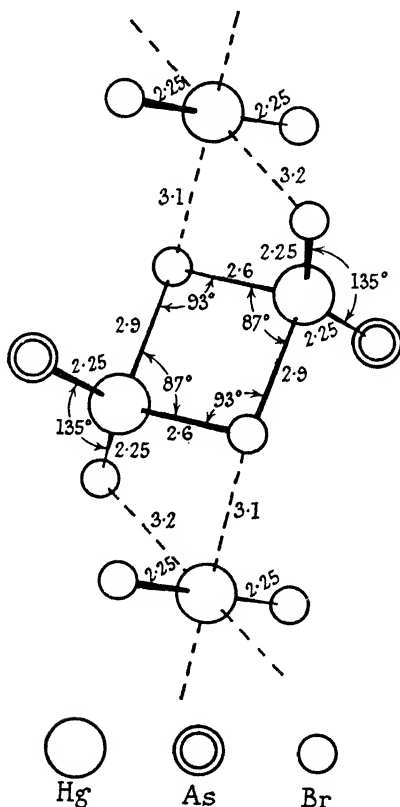
distances and angles are given. The distortion in the bridged part of the complex is probably due to attractions between mercury and bromine atoms shown joined by the broken lines, so that these mercury atoms become surrounded by a distorted octahedron of six bromine atoms, two being directly bound at 2·25 A., and the remaining four contributed by neighbouring bridged molecules at the greater distances of 3·1 and 3·2 A. A similar distorted octahedron has been observed in NH_4HgCl_3 [39] and in $HgBr_2$.[40] $(Et_3As)_2(HgI_2)_3$

[39] H. Harmsen, *Z. Krist.*, 1939, **100**, 208.
[40] H. J. Verweel and J. M. Bijvoet, *ibid.*, 1931, **77**, 122.

is quite different, and it is possible that this complex has the bridged structure (IV).

$$\text{Et}_3\text{As} \diagdown \underset{\nwarrow}{\text{Hg}} \diagup \overset{\text{I}}{\underset{\text{I}}{}} \diagdown \underset{\nwarrow}{\text{Hg}} \diagup \overset{\text{I}}{\underset{\text{I}}{}} \diagdown \underset{\nwarrow}{\text{Hg}} \diagup \overset{\text{AsEt}_3}{\underset{\text{I}}{}}$$

(IV.)

$$\text{R}_3\text{P} \rightarrow \text{Cd} \begin{matrix} \text{Br} \\ \leftarrow\text{Br} \\ \text{Br} \end{matrix} \text{Cd} \begin{matrix} \text{PR}_3 \\ \text{Br} \\ \text{PR}_3 \end{matrix}$$

(V.)
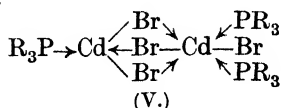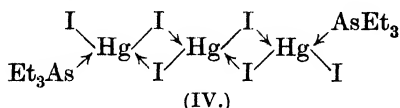
The structures of complexes of the type (d) and (e) are also uncertain, but a space-group determination in the case of $(\text{Bu}_3\text{P})_3(\text{CdBr}_2)_2$ shows that it cannot be a molecular lattice of $2(\text{Bu}_3\text{P})_2\text{CdBr}_2$ and $(\text{Bu}_3\text{P})_2(\text{CdBr}_2)_2$ and the structure (V) has been suggested. Here one of the cadmium atoms is 4-covalent at the centre of a tetrahedron, and the other 6-covalent at the centre of an octahedron, the two polyhedra having a triangular face in common.

G. C. H.

5. Organic Structures.

Phthalocyanines and Related Structures.—X-Ray studies have been carried out on a number of new compounds in this series during the year. Very detailed analyses have already been described for phthalocyanine itself [1] and its nickel derivative,[2] and cell dimensions and space group determinations are available for the beryllium, manganese, iron, cobalt, and copper compounds.[3] The figures show that all these crystals are very closely isomorphous, and hence the main conclusions regarding molecular structure and packing which have been deduced for the parent substance must apply to all these derivatives.

The new structures described are those of platinum phthalocyanine [4] (complete structure determination, see below), tetrabenztriazaporphin (I),[5] tetrabenzmonazaporphin (II) [6] and tetrabenzporphin (III) [6] (cell dimensions and space groups). The last three compounds are of interest because they represent a gradual approach from the phthalocyanine to the natural porphyrin structures, the linking nitrogen atoms of the great ring being replaced by one, three, and finally four methin groups. The synthesis of these compounds has been carried out, and their homogeneity established by the work of R. P. Linstead and others.[5, 7]

[1] J. M. Robertson, *J.*, 1936, 1195.

[2] J. M. Robertson and (Miss) I. Woodward, *J.*, 1937, 219.

[3] R. P. Linstead and J. M. Robertson, *J.*, 1936, 1736.

[4] J. M. Robertson and (Miss) I. Woodward, *J.*, 1940, 36.

[5] P. A. Barrett, R. P. Linstead, G. A. P. Tuey, and J. M. Robertson, *J.*, 1935, 1809.

[6] (Miss) I. Woodward, *J.*, 1940, 601.

[7] P. A. Barrett, R. P. Linstead, F. G. Rundall, and G. A. P. Tuey, *J.*, 1940, 1079; see also *Ann. Reports*, 1937, **34**, 369.

The crystal structures of these new macrocyclic pigments are of special interest, because only in the case of (I) is the phthalocyanine

(I.)

(II.)

(III.)
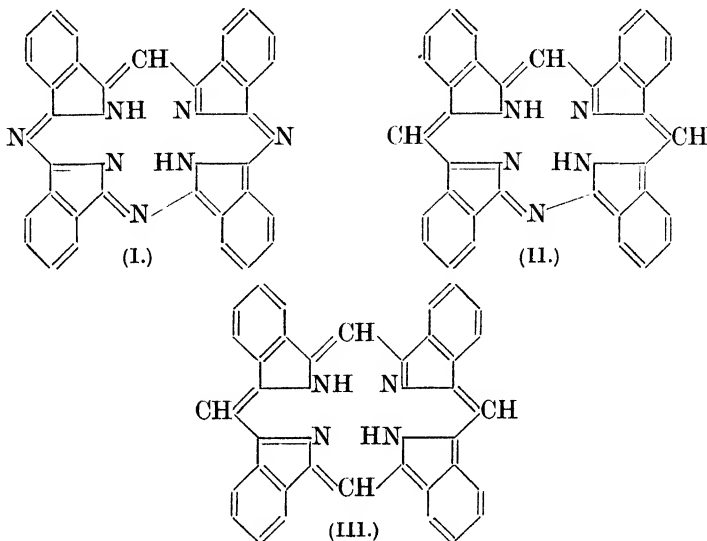
type of structure maintained.   The further replacement of the nitrogen atoms in (II) and (III) has apparently sufficient effect on the molecular packing completely to alter the arrangement—a surprising conclusion in view of the great stability of the normal phthalocyanine structure.   There is little likelihood of any appreciable change in the structures of the molecular frameworks, the chemical evidence being fairly conclusive in this connection.   The same approximate molecular dimensions being therefore assumed, the cell dimensions indicate that in (II) and (III) the molecular planes must be inclined at about 60° to the (010) crystal plane, as against 44° in phthalocyanine itself.   The intensity data indicate that certain other changes in orientation probably occur as well.   The molecules (I) and (II), like the symmetrical compounds, are found to display a centre of symmetry in the crystal.   However, this is no doubt merely a statistical centre of symmetry, due to a random distribution of the molecules with respect to the unique groups.[5]

The detailed structure analysis of platinum phthalocyanine [4] is of interest in several connections.   Here again the structure is found to differ from the normal phthalocyanine type, but in the opposite sense to that of (II) and (III).   The molecules are now less steeply inclined to the (010) plane, the angle being only 26·5° against the normal one of 44°.   All these different structures are probably governed to some extent by the amount of clearance between neigh-

bouring atoms in overlying molecules, and the three distinct struc-
tures probably represent three distinct maxima in this connection.
As the molecular structures themselves are so closely similar, it is
possible that these variations are all potential polymorphic modifica-
tions of one fundamental structure, although no actual transition for
any one compound has yet been observed.

*Platinum phthalocyanine.   The planar molecule is inclined at 26·5° to the
projection plane.   Contour lines at one electron per A.² except at the centre,
where the increment is 20 electrons per line.   The one-electron line is dotted.*

The results of the Fourier analysis of the platinum phthalocyanine
structure are shown in the contour map.   The dimensions of the
molecule are found to be very closely similar to those already
described for the other phthalocyanines, except that the nitrogen–
metal distances have now increased to about 2·01 A. as compared
with 1·92 A. and 1·83 A. in the metal-free and the nickel compound

respectively. This is no doubt due to the increased radius of the platinum atom.

The chief interest of this determination, however, lies in the method of analysis employed. It depends upon the presence of an extremely heavy atom in the molecule, whose contribution to the structure factor for every plane is greater than that of all the other atoms combined. Briefly, unknown differences in phase are in this way converted into differences in amplitude which can be measured. The resulting Fourier synthesis thus becomes equivalent to the well-known Patterson synthesis, but the result is a direct picture of the structure instead of its vector representation.

It is not necessary that the atomic number of the heavy atom should exceed the sum of the atomic numbers of all the other atoms, as might at first be supposed, for the swamping effect on all the structure factors to be complete. The contributions from these other atoms tend to cancel each other out, and only a comparatively small residual factor is finally left to be balanced by the heavy-atom contribution. It thus becomes possible to foresee the application of the method to very large molecules indeed, such as the natural porphyrins, or even to some of the natural protein structures.[8]

The method is thus of wide application, and the paper under discussion is a critical test of it and a study of the difficulties which arise in its application. These are chiefly concerned with the necessity for accurate intensity measurement, and with false detail which arises owing to non-convergence of the F series; but with suitable precautions the resolution of even the light carbon atoms is fairly good, as the figure shows, and the maximum uncertainty in their positions is about $\pm 0 \cdot 1$ A. Even this figure can be considerably improved in most parts of the structure when calculated allowances are made for false diffraction effects, etc.

Another interesting point about this work is the amount of material used in the analysis. It consisted of a single crystal weighing $0 \cdot 0095$ mg.

Acetamide.—A very full investigation has been carried out by F. Senti and D. Harker [9] of the crystal structure of the rhombohedral form of acetamide. It is a complicated structure in the sense that there are 18 molecules in the unit cell (space group C_{3v}^6–$R3c$), and its complete solution with a determination of all the atomic positions represents a considerable achievement. It is a pity, however, that in such a thorough analysis the intensities cannot be determined more quantitatively. In the present instance they are determined

[8] J. M. Robertson, *Nature*, 1939, **143**, 75.
[9] *J. Amer. Chem. Soc.*, 1940, **62**, 2008.

by the oscillation photographic method and visual estimation from selected standards.

The analysis is carried through by a careful application of the well-known Patterson and Harker vector methods, and it includes an interesting study of the refinement of parameters by Fourier series methods in a structure which does not contain centres of symmetry, and in which the phase constants may, therefore, have any fractional values. (Another such structure which has been analysed quantitatively is resorcinol.[10]) It is found that convergence to the true structure is, nevertheless, quite rapid.

The acetamide molecules are found to be planar, as would be required from either of the resonance structures (IV) or (V). The accuracy claimed is considerable, and it is stated that the deviation of any atom from the median plane through the molecule must be less than 0·01 A.

$$(IV.) \quad CH_3-C\diagdown_{NH_2}^{O} \qquad\qquad CH_3-C\diagdown_{NH_2^+}^{O^-} \quad (V.)$$

The interatomic distances are those that might be expected for the structure : $C-O = 1·28$ A., where the resonance is of the same type as in the carboxylic acids, $C-CH_3 = 1·51$ A., and $C-NH_2 = 1·38$ A. The possible uncertainty in all these values is given as about $\pm 0·05$ A. The resonance effect has certainly not equalised the valency angles, the CH_3-C-NH_2 angle being 109° and the other two 122—129°.

In the crystal the planar molecules of acetamide are arranged in rings of six, adjacent molecules in the ring being held together by $N-H \cdots O$ bridges whose mean length is about 2·86 A. This relatively close binding, of course, accounts for the high melting point and boiling point of the substance, as compared with acetone, for example. From the directions of these hydrogen bridges it can be concluded that the $N-H$ bonds lie in the plane of the molecule. Other molecular contacts are of the residual or van der Waals kind.

Dicyandiamide.—A very interesting and complete structure determination has now been carried out by E. W. Hughes on the dimer of cyanamide.[11] The work clearly eliminates the possibility of cyclic structures, and it is shown that the positions of the atoms

$$\overset{3}{N}\!\!\equiv\!\!\overset{1}{C}\!\!-\!\!\overset{4}{N}\diagdown_{\overset{5}{H_2N}\diagup}^{\overset{2}{}\overset{6}{}}\!\!\!C\!\!-\!\!NH_2 \qquad {}^-N\!\!=\!\!C\!\!=\!\!N\diagdown_{H_2N\diagup}C\!\!=\!\!NH_2^+ \qquad {}^-N\!\!=\!\!C\!\!=\!\!N\diagdown_{{}^+H_2N\diagup}C\!\!-\!\!NH_2 \quad .$$
$$\qquad\quad (VI.) \qquad\qquad\qquad\qquad (VII.) \qquad\qquad\qquad\qquad (VIII.)$$

correspond to a molecule which is a resonance hybrid, chiefly between the structures (VI), (VII), and (VIII). Thus in the guanidine group

[10] J. M. Robertson, *Proc. Roy. Soc.*, 1936, **157**, *A*, 79.
[11] *J. Amer. Chem. Soc.*, 1940, **62**, 1258.

the double bond resonates to a certain extent into all possible positions.

The planarity of the guanidine group and the linearity of the cyanimino-group have been established within narrow limits, the probable error in atomic positions in this analysis being given as $\pm$ 0·015 A., and the maximum possible error in bond lengths estimated at about $\pm$ 0·04 A. The cyanimino-group appears to deviate only slightly from the plane of the guanidine group, the movement corresponding to a rotation about the $=N-C\equiv$ bond of 2°.

The interatomic distances are as follows, the numbers referring to the atoms as shown in (VI) : 1–3 = 1·22 A., 1–4 = 1·28 A., 2–4 = 1·36 A., 2–5 = 1·37 A., 2–6 = 1·34 A.

The packing of the molecules is found to be dominated by hydro-gen-bond formation, one of these bonds being of the rare bifurcated type previously noted in the case of glycine.[12] The five distinct hydrogen bonds in the present structure have lengths varying from 2·94 to 3·15 A., and are thus of a rather weak type, but they represent something definitely stronger than the residual van der Waals attractions, and they undoubtedly govern the orientations of the molecules relative to each other.

Some of these bonds are directed towards the terminal nitrogen of the cyanimino-group. Now the structure (IX), with only one

(IX.)   : $N\equiv C-\overset{..}{N}$ $^{-}\overset{..}{\overset{..}{N}}=C=\overset{..}{N}$ (X.)

unshared electron pair on the terminal nitrogen, could only give rise to very weak hydrogen bonds, as in the case of ammonia, where a similar situation prevails; but the alternative structure with two unshared pairs (X) would permit much stronger hydrogen bonds to be formed, and it is thought that this structure consequently makes a larger contribution to the normal state, the final result being that the loss in resonance energy is more than made up by the gain in energy of the hydrogen bonds.   J. M. R.

G. C. Hampson.
J. M. Robertson.
J. C. Speakman.
A. R. Ubbelohde.

[12] *Ann. Reports,* 1939, **36,** 181.

ORGANIC CHEMISTRY.

1. INTRODUCTION.

THE present trend of aliphatic chemistry is being greatly influenced by developments in the petroleum industry. Branched-chain paraffins are now being synthesised and studied with the object of identifying the constituents of fuels and also of discovering compounds of high "anti-knock value." The great industrial importance of polymerisation (*e.g.*, of ethylene to *iso*butene) and of "alkanation" (*e.g.*, addition of *iso*butane to *iso*butene in presence of sulphuric acid) has initiated many researches. Advances in the technique of fractional distillation have made pure paraffins readily accessible, and these are a rich source of aliphatic compounds. Olefins are even more useful; propylene hydrates to *iso*propyl alcohol, which on catalytic oxidation gives acetone; at 400—600° halogens substitute, propylene thus giving allyl bromide or chloride, and by this route glycerol is synthesised. Higher paraffin fractions (10 to 16 carbon atoms) are a source of detergents. The sulphonic acids may be obtained by direct sulphonation; halogenation and hydrolysis lead to alcohols (mainly secondary), which are converted into sulphuric esters; both sulphonic acids and sulphuric esters have received considerable attention.

Reference is also made in the aliphatic section of this Report to recent progress in the isolation and study of individual fatty acids from natural fats. Many facts bearing on the problem of the biosynthesis of fatty acids have emerged, and perhaps the most important development is the synthesis of stearic acid from acetaldehyde (*via* crotonaldehyde). One of the plant wound-hormones,[1] traumatic acid, is a decenedicarboxylic acid, and has been synthesised. The preparation of $\alpha\alpha$-dialkyl long-chain acids whose surface films resemble those of phthioic acid (from tubercle bacilli) is reported. Pantothenic acid,[2] the "chick anti-dermatitis factor" present in liver, has been degraded to β-alanine and the lactone of $\alpha\gamma$-dihydroxy-$\beta\beta$-dimethylbutyric acid; the vitamin has been synthesised.

The evidence relating to the two mechanisms (unimolecular and bimolecular) of aliphatic substitution, up to the end of 1938, was summarised in the Report for that year. The correctness of the view there outlined has now been confirmed. In cases where one reagent is the solvent (*e.g.*, hydrolysis in an aqueous medium), the proof of the unimolecular mechanism depended upon observations

[1] See *Ann. Reports*, 1939, **36**, 368.   [2] *Ibid.*, p. 344.

of the effects of changes in the structure of the compound in which substitution occurs and in the nature of the substituting agent and of the solvent; in certain instances the influence of solvent changes upon the product, and the stereochemical course of the substitution, also provided a guide to the reaction mechanism. This evidence has now been supplemented by a direct kinetic demonstration of the unimolecular character of a number of solvolytic substitutions. A more detailed consideration of the unimolecular mechanism indicated that certain deviations from accurately first-order kinetics should appear when the mechanism is unimolecular; these have been observed, and the effects of added salts upon the reaction rate and upon the products are in harmony with the requirements of the unimolecular mechanism. In the course of this work, evidence of the conjugation of alkyl groups with the aromatic nucleus has been found.

The mechanisms of esterification and ester hydrolysis constitute an old problem. It has now been shown, by four methods, that hydroxyl from the acid, or alkoxyl from the ester, appears in the water or alcohol formed; i.e., fission occurs in accordance with the schemes

$$R \cdot CO \cdot \overline{OH + H}OAlk \longrightarrow R \cdot CO \cdot OAlk + H_2O$$
$$R \cdot CO \cdot \overline{OAlk + H}OH \longrightarrow R \cdot CO \cdot OH + HOAlk$$
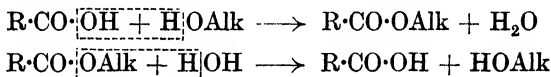
Other mechanistic details have also been studied; several kinetic investigations of the esterification of the saturated aliphatic acids and of the hydrolysis of their esters have been recorded and the results interpreted. Condensations of carbonyl compounds were considered in last year's Report, and have therefore not been dealt with again. It is interesting to record, however, that several examples of these condensations in presence of boron fluoride or aluminium chloride have been found.[3] Their mechanisms have also been further discussed;[4] the mechanism of the reaction of benzaldehyde with acetophenone has been considered in the light of new kinetic measurements[5] which point to the conclusion that substituents in the aldehyde molecule influence mainly the energy of activation, while groups in the acetophenone change the P term of the kinetic equation $k = PZe^{-E/RT}$.

Although the triphenylmethyl radical was first prepared forty years ago, many points in the chemistry of such free radicals have remained obscure, and notable advances have recently been made in the elucidation of the reactions of alkyl-substituted triphenyl-

[3] D. S. Breslow and C. R. Hauser, *J. Amer. Chem. Soc.*, 1940, **62**, 2385, 2389, 2611.

[4] C. R. Hauser *et al.*, *ibid.*, pp. 62, 593, 1763.

[5] (Miss) E. Coombs and D. P. Evans, *J.*, 1940, 1295.

methyls which show unexpected instability.   It has been found that
p-alkyltriphenylmethyls readily undergo disproportionation to give
the corresponding methane (I) and a quinonoid hydrocarbon (II) :

$$2(CH_2R\cdot C_6H_4)_3C- \longrightarrow (CH_2R\cdot C_6H_4)_3CH +$$
(I.)
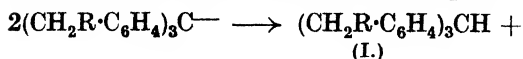
$$CHR=\!\!\!\left\langle\underline{\quad\quad}\right\rangle\!\!\!=C(C_6H_4\cdot CH_2R)_2$$
(II.)
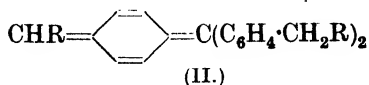
The *p-tert.*-butyl radical, where no such disproportionation is
possible, is stable.   Halogenated triphenylmethyls have presented
special difficulties owing to the reactivity of the nuclear halogen with
the metal used in the preparation of the radical, which gives rise to
a secondary radical such as (III).   Contrary to expectation, the
nuclear halogen in *p*-fluorotriphenylmethyl is more reactive than
that in triphenylfluoromethane, whereas the reverse is the case for
the corresponding bromo-compound.   Results of considerable
interest have also been obtained by the study of the penta-aryl-
ethanes, which can dissociate, giving a mixture of triarylmethyl and
diarylmethyl radicals.   Work upon the magnetic susceptibilities of
free radicals has shown that, when two tervalent carbon atoms are
attached to the 4 : 4′-positions in a diphenyl system as in (IV), the
compound is diamagnetic and exists in the quinonoid form (V), but
the corresponding 3 : 3′-disubstituted derivative (VI) is paramag-
netic like the triarylmethyl radicals; if the radical is non-planar

(III.)   (IV.)   (V.)   (VI.)
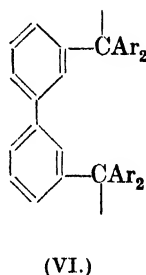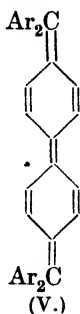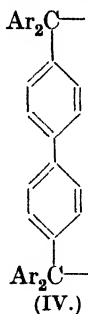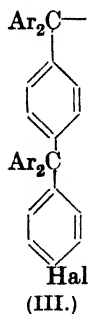
owing to the presence of *ortho*-substituents, paramagnetic properties
are shown even when the tervalent carbon atoms are attached to the
4 : 4′-positions.

Gaseous thermal and photochemical reactions which are known
to involve the primary formation of free radicals have been the
subject of numerous studies; observations of the gaseous nitration
of aliphatic hydrocarbons are of both theoretical and practical
interest, and are in good agreement with the free-radical view.
The presence of free alkyl radicals in the liquid phase was demon-

strated some time ago in the photolysis of aldehydes and ketones in hydrocarbon solvents, and aryl radicals are formed in the decompositions of diazobenzene chloride, diazobenzene hydroxide, *syn*-diazobenzene cyanide, nitrosoacetanilide, benzeneazotriphenylmethane, dibenzoyl peroxide, and their derivatives.[6]   The alkyl and aryl radicals are found to display many features in common, notably in their reactions with hydrocarbon solvents; examples have been recorded of attack by radicals on metals, and evidence has been obtained of the addition of radicals to double bonds.   There is also evidence of the participation of free radicals in certain Claisen rearrangements and in the Wurtz and Fittig reactions, and it is likely that certain reactions of Grignard compounds also involve free radicals.   Atomic chlorination by means of the peroxide-catalysed reaction with sulphuryl chloride provides examples of abnormal aliphatic substitution comparable with the abnormal aromatic substitution reactions previously attributed to aryl radicals.

One of the most interesting developments in carotenoid chemistry during the past five years has been the discovery and examination of the spontaneous isomerisation which occurs in solutions of all carotenoids (especially at elevated temperatures or in the presence of iodine), a phenomenon which has important repercussions on both the identification and the technique of working with these pigments; although conclusive evidence is not yet available, the phenomenon would appear to be due to geometrical isomerism.   By oxidation with alkaline permanganate under carefully controlled conditions the stepwise degradation of several carotenoids has been achieved, the aldehydes obtained providing valuable spectroscopic data and also information concerning the relationship between constitution and provitamin A activity.   Considerable interest has been aroused by the discovery that the polyene acid crocetin plays a fundamental part in the copulation of the male and the female gametes of *Chlamydomonas eugametos*.   A feature of the work on the identification of pigments from natural sources has been a tendency to undertake a systematic study of particular groups, with the result that certain regularities in pigmentation have become apparent; in particular, much attention has been devoted to such studies of the algæ and of the leaf xanthophylls.   Recent researches have shown that astaxanthin, and not astacene, is the characteristic pigment of the Crustaceae, the latter pigment being formed from the labile astaxanthin by oxidation during hydrolysis.

Several authors have discussed the precise mode of linking of the imino-hydrogen atoms in the free porphyrins, and of the metallic atoms in their " salts."   The catalytic properties of the latter have

* *Ann. Reports*, 1937, **34**, 282.

been compared with those of the oxidases and catalase. A series of tetrabenzazaporphins—transitional between the phthalocyanine and porphyrin types—has been thoroughly investigated, and the synthesis placed on a more rational basis by a study of *iso*indoles as intermediate stages. H. Fischer has proposed for chlorophyll a modified formula with the " extra hydrogens " in ring IV, based on the results of oxidative degradation; a corresponding structure is assigned to bacteriochlorophyll, now recognised as a tetrahydroporphin. Substantial progress has been made in the synthetic approach to chlorophyll. There is now some evidence that natural hæmin is not homogeneous, but may contain 25% of hæmin II, which has the same orientation as copro- and uro-porphyrins I.

Since the bile pigments were last reviewed in 1933, notable advances have been made in methods of synthesis, especially of unsymmetrically constituted materials. The degradation of porphyrins to bilirubinoids has been effected by several purely chemical as well as biological methods; hydroxylated dipyrrylmethenes have been recognised as further stages of the breakdown, and as responsible for the " pentdyopent " reaction. A reduced bilirubinoid structure is assigned to stercobilin.

The most spectacular achievement in steroid chemistry during the period under review is the total synthesis of the naturally occurring sex hormone *d*-equilenin and its three stereoisomerides. Great progress has been made in the development of methods for the conversion of androstane into pregnane derivatives; new partial syntheses of progesterone and deoxycorticosterone from dehydroandrosterone have been reported. One of the more promising methods for the preparation of 20-ketopregnane derivatives (*e.g.*, progesterone) appeared to be the hydration of the readily available 17-hydroxy-17-ethinylandrostane intermediates (I) by the mercuric oxide–boron fluoride method. Although hydration occurs, it has been established that the reaction is accompanied by ring-D enlargement with formation of the 17-keto-D-homoandrostane derivative (II).

(I.)   (II.)   (III.)   (IV.)
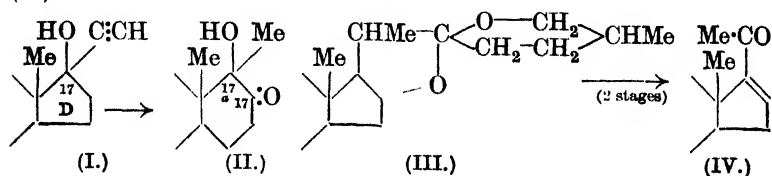
Important advances have been made in the chemistry of the steroid sapogenins, the side chain of which has been shown to contain a protected (ketal) carbonyl group (III). The ready isomerisation of the sapogenins to ψ-sapogenins by means of acetic

anhydride, and the facile oxidation of ψ-sapogenins to 20-keto-Δ^{16}-pregnene intermediates (IV), have opened up a remarkably simple route to the pregnane (or *allo*pregnane) series. The structures of several of the less abundant sterols such as brassicasterol, α-spinasterol and zymosterol have been determined.

Two independent sets of phenomena have been correlated with the relative basic or acidic characters of heterocylic rings. Benzopyrans in spiro-condensation with heterocyclic nuclei can undergo reversible intramolecular ionisation with very different degrees of facility, yielding phenol-betaines in which the pyran ring is ruptured and the second nucleus now contains an 'onium atom. The intense colour of cyanine dyes is attributed to resonance between structures in which the positive ionic charge is associated with different nitrogen atoms. In the bases of which the dyes are quaternary salts, one canonical structure contains negatively-charged bicovalent nitrogen, and here the degree of resonance and observed depth of colour are usually, but with significant exceptions, diminished relatively to those of the salts. The dimensions of several heterocyclic nuclei have been determined by electron-diffraction measurements; indications of the participation of states in which a sulphur atom is associated with an electron decet agree with other purely chemical evidence.

Natural products containing oxygen rings have received much attention. Cannabinol has been synthesised by two different methods, and the constitution of homopterocarpin from red sandalwood has been elucidated. Usnic acid probably does not contain the many-membered ring previously ascribed to it, and is represented by a more conventional dibenzofuran formula. Primetin methyl ether has been synthesised, and pedicin is regarded as a benzylidene-coumaranone derived from pentahydroxybenzene.

Syntheses of the glyoxaline alkaloid pilosinine and of *r*-lupinine are recorded. Further progress has been made with the di*iso*quinoline bases of curare, and several alkaloids from various sources prove to be simple benzyl*iso*quinoline derivatives of familiar type. The nitrogenous rings of cevine and the *Solanum* alkaloids have been explored, and cassaine also is a steroid or polyterpenoid derivative which on saponification yields its nitrogen as dimethylaminoethanol. Recent work on the *Strychnos* bases is summarised.

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T. S. STEVENS.
H. B. WATSON.

2. Aliphatic Compounds.

The last three or four years have seen big changes in aliphatic chemistry, and these have been brought about mainly by the conversion of the petroleum industry into a major chemical industry. Petroleum gases (natural gas, and the gases from " cracked " petroleum) are, taken together, a rich source of most of the lower paraffins and olefins. These hydrocarbons, of which many *millions of tons* are handled each year, are becoming the raw materials for the preparation of the lower aliphatic compounds, just as benzene, toluene, and naphthalene have been the starting points in other series. Thus ethyl alcohol has for many years been made cheaply from ethylene ; acetone and glycerol are now made from propylene, methyl ethyl ketone from butylene, and the amyl alcohols from the pentanes ; fatty acids (made by oxidising solid paraffins) can be converted into synthetic fats.

These industrial developments are not only causing a revolution in chemical industry, but are creating many problems for solution by academic chemists. As a further result of this progress many substances previously obtainable only in small quantities are now available by the ton, and in a high state of purity.

All that is intended in this Report is to record some of the more important advances, and to indicate to organic chemists that the range of reagents available in quantity has been considerably widened. Full accounts can be obtained in the technical publications.[1, 2]

Branched Chain and cyclo*Paraffins.*—Investigations into the composition of petroleum and of " cracked " petroleum fractions have required the preparation of pure hydrocarbons for use in the identification of constituents. At the same time the search for fuels of high " antiknock rating " has stimulated research on branched chain and *cyclo*paraffins. In several laboratories, university and industrial, mainly in Holland and America, these hydrocarbons have been synthesised on a large scale by unequivocal methods, and the physical constants have been recorded.

The methods of synthesis are not in themselves new, the most important series of reactions used being represented by the scheme :
ketone, ester, aldehyde (or olefin oxide) $\xrightarrow{\text{R·MgCl}}$ alcohol $\xrightarrow{-\text{H}_2\text{O}}$ olefin $\xrightarrow{+\text{H}_2}$ paraffin. Much use has of course been made of the Grignard reaction in the preparation of the alcohols, but apart from the use of gaseous methyl and ethyl chlorides (from cylinders) the usual

[1] *Annual Review of Petroleum Technology*, 1939, **5**, 184 (F. H. Braybrook); Reports of the Progress of Applied Chemistry.

[2] " The Science of Petroleum " (A. E. Dunstan), Oxford, 1938; " The Chemistry of Petroleum Derivatives " (C. Ellis), New York (Vol. I, 1934; Vol. II, 1937).

rather tedious Grignard technique has had to be retained.   Reduction of the olefins has been much simplified by the introduction of the Raney nickel catalyst and of high-pressure hydrogenation.

Other methods used in these researches are (a) the Wurtz–Fittig reaction, applicable to symmetrical hydrocarbons; (b) interaction of a Grignard reagent with an alkyl chloride in presence of mercuric chloride; (c) reduction of halides with zinc dust and acetic acid; (d) interaction of halides and zinc dialkyls.

For purification the almost universal method is fractional distillation; great advances have in recent years been made in the design of efficient laboratory columns.

There are at least two lists of hydrocarbons and their physical properties;[3] but the compounds recently prepared for the purposes indicated above are as follows :

Pentanes :	*n*-pentane [4, 5]	2-methylbutane [4]
Hexanes :	*n*-hexane [4, 5]	2-methylpentane [4, 18]
	3-methylpentane [4]	2 : 2-dimethylbutane [6, 18]
	2 : 3-dimethylbutane [6, 18]	
Heptanes :	*n*-heptane [7, 5] 3-methylhexane [8]	2-methylhexane [4, 7, 8]
	2 : 3-dimethylpentane [4, 8]	2 : 4-dimethylpentane [4]
	3 : 3-dimethylpentane [4, 8]	2 : 2 : 3-trimethylbutane [4, 6, 18]
	3-ethylpentane [6]	2 : 2-dimethylpentane [8]
Octanes :	*n*-octane [4, 5, 10]	3-methylheptane [4, 10]
	2 : 3-dimethylhexane [4, 9, 10]	2 : 4-dimethylhexane [10]
	2 : 5-dimethylhexane [4, 10, 11]	3 : 4-dimethylhexane [4, 10, 18]
	3-methyl-3-ethylpentane [4, 10]	2-methylheptane [10]
	2 : 2 : 3-trimethylpentane [4, 6, 12, 18]	2 : 3 : 4-trimethylpentane [18]
Nonanes :	*n*-nonane,[5, 13] 2-methyloctane [7, 14]	2 : 3-dimethylheptane [14]
	2 : 6-dimethylheptane [15]	3-ethylheptane [14]
	2 : 2 : 4 : 4-tetramethylpentane [14, 17]	
Decanes :	*n*-decane [5, 16] and 2-, 3-, 4- and 5-methylnonane.[16]	

[3] A. L. Ward and S. S. Kurtz (jun.), *Ind. Eng. Chem. (Anal.)*, 1938, **10**, 559; G. Egloff, " Physical Constants of Hydrocarbons," New York, 1939.

[4] J. P. Wibaut, H. Hoog, S. L. Langedijk, J. Overhoff, and J. Smittenberg, *Rec. Trav. chim.*, 1939, **58**, 329.

[5] B. J. Mair, *J. Res. Nat. Bur. Stand.*, 1932, **9**, 457.

[6] D. B. Brooks, F. L. Howard, H. C. Crafton, *ibid.*, 1940, **24**, 33.

[7] F. C. Whitmore and H. P. Drem, *J. Amer. Chem. Soc.*, 1938, **60**, 2573.

[8] G. Edgar, G. Calingaert, and R. E. Marker, *ibid.*, 1929, **51**, 1483.

[9] F. C. Whitmore and W. L. Evers, *ibid.*, 1933, **55**, 812.

[10] A. Maman, *Compt. rend.*, 1937, **205**, 319.

[11] M. J. Timmermans and (Mme.) Hennant-Roland, *J. Chim. physique*, 1932, **29**, 529.

[12] F. C. Whitmore and K. C. Laughlin, *J. Amer. Chem. Soc.*, 1932, **54**, 4011.

[13] L. Clarke and R. Adams, *ibid.*, 1915, **37**, 2536.

[14] F. C. Whitmore, and H. A. Southgate, *ibid.*, 1938, **60**, 2571.

[15] J. D. White, F. W. Rose (jun.), G. Calingaert, and H. Soroos, *J. Res. Nat. Bur. Stand.*, 1939, **22**, 315.

[16] G. Calingaert and H. Soroos, *J. Amer. Chem. Soc.*, 1936, **58**, 635.

[17] F. L. Howard, *J. Res. Nat. Bur. Stand.*, 1940, **24**, 677.

[18] L. Schmerling, B. S. Friedman, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, 1940, **62**, 2446.

A synthesis which shows both the general method and a special difficulty owing to an isomerisation is that of 2 : 2 : 3-trimethyl-pentane :

$$
\begin{array}{c}
\overset{\text{Me}}{\underset{\text{Me}}{\text{Me·C}-\text{CO}}} \xrightarrow{\text{EtMgCl}} \overset{\text{Me Me}}{\underset{\text{Me OH}}{\text{Me·C}-\text{C·Et}}}
\begin{array}{c}
\nearrow \quad \overset{\text{Me Me}}{\underset{\overset{|}{\text{H}} \ \text{Me}}{\text{Me·C}-\text{C·CH:CH}_2}} \\[2em]
\searrow \quad \overset{\text{Me Me}}{\underset{\text{Me}}{\text{Me·C}-\text{C:CHMe}}} \rightarrow \overset{\text{Me Me}}{\underset{\text{Me}}{\text{Me·C}-\text{CHEt}}}
\end{array}
\end{array}
$$
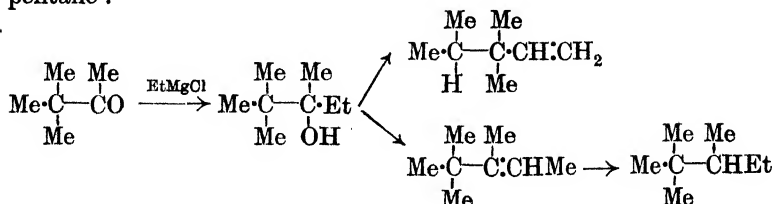
The carbinol resulting from the action of ethylmagnesium chloride on pinacolone has been dehydrated in several ways, but in every case isomerisation also occurred. Refluxing with naphthalene-β-sulphonic acid gave the best results, and the resulting mixture of olefins was partly separated by fractional distillation.[4, 12]   After hydrogenation of the olefin, the paraffin was subjected to thorough fractionation.[4, 6] P. L. Cramer and M. J. Mulligan,[19] however, have shown that in the preparation of 2 : 2-dimethylbutane from pinacolyl alcohol, the isomerisation can be avoided by use of the acetate, which when passed over glass-wool at 400° yields only 3 : 3-dimethyl-Δ^1-butene :

$$
\text{CMe}_3\text{·CHMe·OH} \longrightarrow \text{CMe}_3\text{·CHMe·OAc} \xrightarrow{400°} \text{CMe}_3\text{·CH:CH}_2
$$
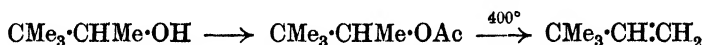
The mechanisms of the pinacol–pinacolone and the Wagner–Meerwein transformations have recently been discussed by H. B. Watson.[20]

Ethylcyclobutane, cyclopentane, methylcyclopentane, cyclohexane, methylcyclohexane and isopropylcyclohexane have been prepared by Wibaut,[4] n-octyl- and n-octadecyl-cyclohexane by Waterman.[21]

The preparation of tert.-butyl- and tert.-amyl-cyclopentanes has been reported.[22]   Failure of tert.-butylmagnesium chloride and cyclopentanone to yield tert.-butylcyclopentanol (compare the action of isopropylmagnesium iodide[23]) led to a search for another intermediate.   This was found in the commercially available p-tert.-butylphenol.   Hydrogenation gave 4-tert.-butylcyclohexan-1-ol, which on oxidation with nitric acid and ammonium vanadate[24] gave β-tert.-butyladipic acid.   Cyclisation of the adipic acid (barium salt) yielded 2-tert.-butylcyclopentanone; hydrogenation to the carbinol, dehydration and reduction led to tert.-butylcyclopentane.

[19] J. Amer. Chem. Soc., 1936, **58**, 373.   [20] Ann. Reports, 1939, **36**, 196.
[21] H. I. Waterman, J. J. Leenderste, and D. W. van Krevelen, J. Inst. Petroleum, 1939, **25**, 801.
[22] H. Pines and V. N. Ipatieff, J. Amer. Chem. Soc., 1939, **61**, 2728.
[23] H. Meerwein, Annalen, 1914, **405**, 155.
[24] J. Niederl and R. A. Smith, J. Amer. Chem. Soc., 1937, **59**, 715.

Olefins.—Ethylene is oxidised (with oxygen at 350° in presence of finely divided silver) to ethylene oxide,[25] from which glycol chlorhydrin, glycol and glycol ethers can be made, thus reversing the previous order. In recent years the reaction between ethylene oxide and hydrogen sulphide with the formation of $\beta\beta'$-dihydroxydiethyl sulphide ("thiodiglycol") has not been overlooked.[26] Besides its value in organic synthesis ethylene oxide is effective as an insecticide. Other oxides are used in industry as intermediates : propylene oxide is isomerised by acids to propaldehyde, and *iso*butylene oxide similarly yields *iso*butyraldehyde.[2, p. 2784]

Dehydrogenation of olefins is receiving a good deal of attention. If the butenes are passed over the oxide of chromium, molybdenum or vanadium on alumina at 600—650° (at 0·25 atmosphere pressure) an 18% yield of butadiene is obtained. 3-Methyl-Δ^1-butene similarly gives 21% of isoprene [27] (the butadiene content of the butene fraction of "cracked" petroleum amounts to 12—14%). With the higher members of the series the reaction goes further. Ring closure and aromatisation of paraffins and olefins (above C_6) take place when the aliphatic compound is passed over amorphous chromium oxide at 400° : [28]

$$\text{paraffin} \rightleftharpoons \text{olefin} + \text{hydrogen}$$
$$\searrow \quad \swarrow$$
$$\text{aromatic} + \text{hydrogen}$$
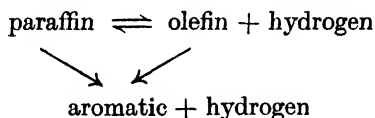
n-Hexane yields benzene, *n*-heptane or 2-methylhexane yields toluene, *n*-octane mainly *o*-xylene, and *n*-nonane yields mainly *o*-methylethylbenzene.[29] This reaction may prove of great value both as a source of aromatic hydrocarbons and as a means of raising the "antiknock value" of fuels.

Polymerisation of propylene with dilute phosphoric acid is a decidedly stepwise process, the dimeride, trimeride, and tetrameride having been isolated.[30] Butenes have been polymerised in the cold to materials with rubber-like physical properties, but with much less

[25] Brit. Pat. (1935), 462,487.
[26] A. E. Chichibabin, French Pat. (1934), 769,216; D. F. Othmer and D. Q. Kern, *Ind. Eng. Chem.*, 1940, **32**, 160.
[27] A. V. Grosse, J. C. Morrell, and J. V. Mavity, *Ind. Eng. Chem.*, 1940, **32**, 309.
[28] B. Moldawski and H. Kamuscher, *Compt. rend. Acad. Sci. U.S.S.R.*, 1936, **1**, 355; Brit. Pat., 409,312; 466,609.
[29] H. Hoog, J. Verheus, and F. J. Zuiderweg, *Trans. Faraday Soc.*, 1939, **35**, 993; K. C. Pitkethly and H. Steiner, *ibid.*, p. 979; A. V. Grosse, J. C. Morrell, and W. J. Mattox, *Ind. Eng. Chem.*, 1940, **32**, 528.
[30] L. A. Monroe and E. R. Gilliland, *Ind. Eng. Chem.*, 1938, **30**, 58.

chemical reactivity. Owing to the absence of unsaturation these materials are resistant to the action of ozone.[31]

Large quantities of *iso*butene arise from the cracking of petroleum and can be converted into liquid hydrocarbons of high "antiknock rating ". The C_4 fraction is separated by distillation; treatment with 65% sulphuric acid removes the *iso*butene more than 100 times as fast as it does the Δ^1- or Δ^2-butene. Heating the sulphuric acid layer to about 100° causes polymerisation (dimerisation) of the *iso*butene; the product separates as an oily layer and the acid can be used again.[32] Instead of sulphuric acid, copper cadmium phosphate can be used for this polymerisation.[33] The product, di*iso*butene, is then reduced catalytically to " *iso*octane ", 2 : 2 : 4-trimethylpentane. This substance,

$$2CMe_2{:}CH_2 \longrightarrow CMe_3{\cdot}CH_2{\cdot}CMe{:}CH_2 \longrightarrow CMe_3{\cdot}CH_2{\cdot}CHMe_2$$

because of its exceptionally small tendency to " knock " in engines, is taken as the standard and given the antiknock rating or " octane number " of 100. (Another aliphatic compound of high " octane number " is di*iso*propyl ether.)

A process which makes use of both *iso*butene and *iso*butane and avoids the necessity for a hydrogenation of the product is the remarkable " alkanation " * which occurs in presence of cold sulphuric acid. When *iso*butene, *iso*butane and 97% sulphuric acid are stirred at 20°, the pressure falls during 90 minutes from 50 lb. per sq. in. to atmospheric, and a high yield of "*iso*octane" results.[33, 34]

$$CHMe_3 + CH_2{:}CMe_2 \longrightarrow CMe_3{\cdot}CH_2{\cdot}CHMe_2$$
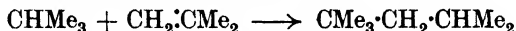
A similar reaction has been shown to occur with, on the one hand, the simpler *iso*paraffins, *iso*butane, *iso*pentane, 2-methylpentane, and, on the other hand, with the olefins propene, Δ^1- and Δ^2-butene, *iso*butene, and the di- and tri-merides of *iso*butene. No convincing explanation of the reaction has yet appeared.

The action of sulphuric acid on olefins and on branched chain paraffins is complex. W. R. Ormandy and E. C. Craven [34a] have

[31] W. J. Sparks, I. E. Lightbown, L. B. Turner, P. K. Frohlich, and C. A. Klebsattel, *Ind. Eng. Chem.*, 1940, **32**, 731; R. M. Thomas, I. E. Lightbown, W. J. Sparks, P. K. Frohlich, and E. V. Murphree, *ibid.*, p. 1283.

[32] W. J. Sparks, R. Rosen, and P. K. Frohlich, *Trans. Faraday Soc.*, 1939, **35**, 1040; F. C. Whitmore, *Ind. Eng. Chem.*, 1934, **26**, 94.

[33] A. E. Dunstan, *Nature*, 1940, **146**, 186; S. F. Birch and A. E. Dunstan, *Trans. Faraday Soc.*, 1939, **35**, 1013.

[34] Brit. Pat. (1936–1938) 479,345; S. F. Birch, A. E. Dunstan, F. A. Fidler, F. B. Pim, and T. Tait, *J. Inst. Petroleum*, 1938, **24**, 308; *Ind. Eng. Chem.*, 1939, **31**, 1079.

[34a] *J. Inst. Petroleum*, 1927, **13**, 311, 844. But see V. N. Ipatieff and H. Pines, *J. Org. Chem.*, 1936, **1**, 464.

* Drs. A. E. Dunstan and S. F. Birch (private communication) prefer this term to " alkylation," now being used by American writers.

observed a kind of disproportionation (which they term " hydropoly-merisation ") when an olefin and sulphuric acid give rise to a paraffin and a highly unsaturated product.

Because of the great demand for esters as solvents for lacquers the preparation of esters from olefins has been investigated. When an olefin is stirred and heated under pressure with acetic and sulphuric acids at 60° for two hours, an acetate results; propylene yields *iso*propyl acetate, Δ^1- and Δ^2-butene give *sec.*-butyl acetate; *iso*-butene yields *tert.*-butyl acetate.[35] (In practice the butene–butane fraction is used in the preparation of *sec.*-butyl acetate.)

The tertiary olefin, trimethylethylene, reacts readily with phenol in presence of sulphuric acid to yield *p-tert.*-amylphenol (which with formaldehyde gives a resin suitable for incorporation in drying oils). Under the same conditions secondary olefins, such as Δ^2-pentene, yield stable phenol ethers which rearrange only with difficulty.[2, p. 2799]

Halogenation of Olefins.—An obvious way to use the large quantity of propylene available would be to convert it into glycerol. It was soon realised, however, that the essential intermediate was allyl chloride, and many ways of obtaining this from propylene were tried.[36] *iso*Butylene, at the ordinary temperature, does not *add* chlorine appreciably, but by substitution yields methallyl chloride (β-methylallyl chloride, $CH_2{:}CMe{\cdot}CH_2Cl$). This reaction of *iso*-butylene at a low temperature is exceptional, however, and really misled the earlier investigators. It was discovered finally that, when propylene was chlorinated at 400—600°, almost exclusive substitution occurred.

$$CH_3{\cdot}CH{:}CH_2 \xrightarrow[500°]{Cl_2} \underset{96\%}{CH_2Cl{\cdot}CH{:}CH_2} + \underset{3\%}{CH_3{\cdot}CCl{:}CH_2} + \underset{1\%}{CH_3{\cdot}CH{:}CHCl.}^{[37]}$$
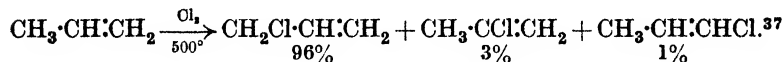
Despite the attendant dangers of this high-temperature exothermic reaction the process is being successfully worked. Allyl chloride (or bromide) and allyl alcohol are now readily available; methallyl chloride and methallyl alcohol are easily obtained from *iso*butene. By various methods, such as the addition of hypochlorite, followed by hydrolysis, allyl chloride is converted into glycerol of high purity, and methallyl chloride into β-methylglycerol.

Chlorination of Paraffins.—According to H. B. Hass, E. T. McBee, and P. Weber [38] the hydrogen atoms in a paraffin are chlorinated in the vapour phase (at 300°) in the ratio, primary : secondary : tertiary

[35] T. W. Evans, K. R. Edlund, and M. D. Taylor, *Ind. Eng. Chem.*, 1938, **30**, 55.

[36] E. C. Williams, *Ind. Eng. Chem., News Edition*, 1938, **16**, 630; B. T. Brooks, *Ind. Eng. Chem.*, 1939, **31**, 515.

[37] H. P. A. Groll and G. Hearne, *Ind. Eng. Chem.*, 1939, **31**, 1530; W. E. Vaughan and F. F. Rust. *J. Org. Chem.*, 1940, **5**, 449, 472.

[38] *Ind. Eng. Chem.*, 1935, **27**, 1190; 1936, **28**, 333.

$= 1 : 3 \cdot 25 : 4 \cdot 43$. These chlorinations are now carried out industrially on a huge scale. To take an example, even in 1937 one plant chlorinated per day 100,000 gallons of the pentane–*iso*pentane fraction from natural gas. For this, 22 tons of chlorine were passed into a 60 mile-per-hour stream of hot pentane vapour, only 3 gallons of pentane and 8 oz. of chlorine being in the reaction zone at one time. Absorption of the hydrogen chloride produced was one of the main problems.[2, p. 2795]

The chlorides so obtained may isomerise immediately after formation and the mixture is difficult to analyse by fractional distillation because of the loss of hydrogen chloride from the tertiary halides. Conversion into the alcohols by heating with sodium oleate and sodium hydroxide solution (emulsifying hydrolysis) is also accompanied by olefin formation. The 50/50 mixture of *n*- and *iso*-pentane used yields a product containing 50—60% of primary alcohols; these are technically more valuable than the secondary alcohols.[2, p. 2796] The aliphatic alcohols thus become available in large quantities not only from the olefins (by hydration) but also from the paraffins; in the C_6 series, *n*-hexyl alcohol, hexaldehyde and hexoic acid are commercial products. Study of the physical properties of the hexyl alcohols has been continued by Havorka.[39] Attention is being paid to the halogenation of higher paraffin fractions mainly with a view to obtaining alcohols whose sulphuric esters may serve as detergents.[40] For example, the paraffin fraction, b. p. 95—100°/15 mm., on chlorination gives a product containing 80—90% of monochlorides. These can be converted into alcohols in 30% yield by heating with sodium oleate solution at 170° for 9 hours.[41] By the action of chlorosulphonic acid the alcohols are converted into sulphuric esters and these into the sodium salts. Unfortunately the value of these salts from the mixture of alcohols is much less than that of primary alcohol derivatives such as sodium lauryl (*n*-dodecyl) sulphate. A. R. Padgett and E. F. Degering[41] synthesised the sulphuric esters of the dodecan-2-, -3-, -4-, -5- and -6-ols; they found that the " foam value " and the ability to lower interfacial tension decreased as the hydroxyl (or ester) group was moved towards the middle of the chain. Solutions of sodium cetyl (C_{16}) and lauryl sulphate show on standing a rapid and then a slow fall in surface tension.[42]

The preparation of aliphatic sulphonic acids from the halides and

[39] F. Havorka, H. P. Lankelme, and I. Schneider, *J. Amer. Chem. Soc.*, 1940, **62**, 1096. See also S. C. Stanford and W. Gordy, *ibid.*, p. 1247.

[40] C. F. Reed, U.S. Pat. (1936) 2,046,090; *Ann. Reports*, 1939, **36**, 233.

[41] *Ind. Eng. Chem.*, 1940, **32**, 204.

[42] G. C. Nutting, F. A. Long, and W. D. Harkins, *J. Amer. Chem. Soc.*, 1940, **62**, 1496.

sulphites has been simplified by S. Zuffanti.[43] As the series is ascended and the alkyl chain becomes longer, the sulphonic acids (in solution) gradually take on the properties of colloidal electrolytes.   In order to explain the properties of these solutions McBain postulates the existence of (a) neutral micelle and (b) ionic micelle.[44]

The Nitration of Paraffins.—Apparently working on the plan of making compounds first and finding a market for them afterwards, the enterprising American chemists have devised a successful process for the manufacture of nitroparaffins.   The n-paraffins are scarcely attacked by nitric acid in the liquid phase, but in the vapour phase at 420° a mixture of nitric acid and paraffin (1 mole of acid to 2 moles of paraffin) reacts in less than one second.[45] (Nitric acid is completely dissociated at 250°.)   The products obtained are those theoretically derivable from the free radicals formed by loss of hydrogen or fission of a C–C bond.   Ethane yields nitroethane (73%) and nitromethane (27%); [46] n-butane yields 2-nitrobutane (50%), 1-nitrobutane (27%), 1-nitropropane (5%), nitroethane (12%), and nitromethane (6%).[46]   Pentane [47] and *iso*pentane [48] have also been nitrated.

The mechanism of the nitration is discussed by R. F. McCleary and E. F. Degering ; [49] the application of the nitroparaffins to organic syntheses is illustrated by C. L. Gabriel.[50]

The nitroparaffins have found uses as solvents for nitrocellulose and lacquers,[45] but their value lies in their varied reactivity and they are becoming most important synthetic intermediates.   Reduction with iron and hydrochloric acid, or catalytically with Raney nickel and hydrogen, gives 90% yield of amine; reduction with stannous chloride or with zinc dust and acetic acid gives the oxime, which on hydrolysis with dilute sulphuric acid gives a 43% yield of the aldehyde.[51] [A series of n-primary amines ($C_6H_{13}\cdot NH_2$ to $C_{18}H_{37}\cdot NH_2$) has been prepared and the boiling points measured under various

[43] *J. Amer. Chem. Soc.*, 1940, **62,** 1044. Compare D. L. Vivian and E. E. Reid, *ibid.*, 1935, **57,** 2559; C. R. Noller and J. J. Gordon, *ibid.*, 1933, **55,** 1090.

[44] E. L. McBain, W. B. Dye, and S. A. Johnston, *ibid.*, 1939, **61,** 3210; E. L. McBain, *Proc. Roy. Soc.*, 1939, *A,* **170,** 415; P. van Rysselberghe, *J. Physical Chem.*, 1939, **43,** 1049.

[45] H. B. Hass, E. B. Hodge, and B. M. Vanderbilt, *Ind. Eng. Chem.*, 1936, **28,** 339.

[46] H. J. Hibshman, E. H. Pierson, and H. B. Hass, *ibid.*, 1940, **32,** 427.

[47] H. B. Hass and J. A. Patterson, *ibid.*, 1938, **30,** 67.

[48] L. B. Seigle and H. B. Hass, *ibid.*, 1939, **31,** 648.

[49] *Ibid.*, 1938, **30,** 64; see also P. G. Stevens and R. W. Schiessler, *J. Amer. Chem. Soc.*, 1940, **62,** 2886.

[50] *Ind. Eng. Chem.*, 1940, **32,** 887.

[51] K. Johnson and E. F. Degering, *J. Amer. Chem. Soc.*, 1939, **61,** 3194.

pressures.[52]   The salts of the amines with organic acids are useful emulsifying agents.]

By the action of concentrated sulphuric acid at 60° the nitro-paraffins yield hydroxamic acids :

$$R{\cdot}CH_2{\cdot}NO_2 \longrightarrow R{\cdot}CH{:}N{\big<}^O_{OH} \longrightarrow R{\cdot}CH{\big<}^{OH}_{NO} \longrightarrow R{\cdot}C{\big<}^{OH}_{NOH}$$
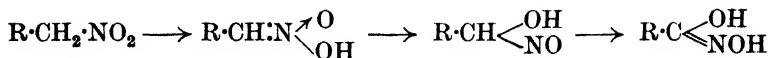
Heating with 85% sulphuric acid takes the reaction further, $R{\cdot}C{\big<}^{OH}_{NOH} \longrightarrow R{\cdot}C{\big<}^{OH}_{O} + NH_2{\cdot}OH$. Thus nitroethane and 1-nitro*iso*butane give 90% yields of acetic and *iso*butyric acid respectively.[53]   As a by-product of this reaction hydroxylamine becomes a cheap reagent.   The reactions with alkali and with chlorine will lead to important products,[50] but the most promising is the condensation with aldehydes.[53a] In presence of sodium carbonate form-aldehyde may react with all the α-hydrogen atoms : $CH_3{\cdot}NO_2 \longrightarrow CH_2(CH_2{\cdot}OH){\cdot}NO_2 \longrightarrow CH(CH_2{\cdot}OH)_2{\cdot}NO_2 \longrightarrow C(CH_2{\cdot}OH)_3{\cdot}NO_2$. The trinitrate of this trishydroxymethylnitromethane is an excellent explosive.   Similarly nitroethane yields the bishydroxymethyl derivative, $CH_3{\cdot}C(CH_2{\cdot}OH)_2{\cdot}NO_2$, the dinitrate of which is also an explosive.   Other aldehydes (and ketones) condense with only one hydrogen atom of the nitroparaffin.   Reduction of the nitro-hydroxy- gives the aminohydroxy-compounds such as 2-amino-2-methylpropane-1 : 3-diol, $CMe(CH_2{\cdot}OH)_2{\cdot}NH_2$;   these are soluble bases which yield with higher fatty acids valuable emulsifying soaps.[50]

Diketen.—The pyrolysis of acetone to keten ($CH_3{\cdot}CO{\cdot}CH_3 \longrightarrow CH_4 + CH_2{:}C{:}O$), followed by reaction with acetic acid to form acetic anhydride, is a well-established process $[CH_3{\cdot}CO_2H + CH_2{:}C{:}O \longrightarrow (CH_3{\cdot}CO)_2O.]$ Keten is much used in industry as an acetylating agent.[54]

Wilsmore,[55] who first prepared keten, found that it polymerised to a lachrymatory liquid, diketen (b. p. 127°), which had many interesting reactions.   The substance is now available commercially in America; although the liquid polymerises on keeping, the solid (m. p. −6·5°) can be kept indefinitely in aluminium containers cooled with solid carbon dioxide.[56]   One of its industrial uses is in the manufacture of acetoacetic esters.   A. L. Wilson (quoted by Boese [56]) proposes the formula (I).

[52] A. W. Ralston, W. M. Selby, W. O. Pool, and R. H. Potts, *Ind. Eng. Chem.*, 1940, **32**, 1093.

[53] S. B. Lippincott and H. B. Hass, *ibid.*, 1939, **31**, 118.

[53a] L. Henry, *Bull. Soc. chim.*, 1895, **13**, 999.

[54] G. H. Morey, *ibid.*, p. 1129.

[55] N. T. M. Wilsmore, *J.*, 1907, **91**, 1938; F. Chick and N. T. M. Wilsmore, *J.*, 1908, **93**, 946; 1910, **97**, 1978.

[56] A. B. Boese (jun.), *Ind. Eng. Chem.*, 1940, **32**, 16.

A few of the reactions are :

$$CH_2\text{:}C\text{——}CH_2 + R\text{·}OH + acid \longrightarrow CH_3\text{·}CO\text{·}CH_2\text{·}CO_2R$$
$$\quad\; O\text{——}CO$$

(I.) $+ Ni/H \longrightarrow CH_3\text{·}CH\text{——}CH_2$ β-butyrolactone
$$\qquad\qquad\qquad\qquad\qquad O\text{———}CO$$

$$+ Ar\text{·}NH_2 \longrightarrow CH_3\text{·}CO\text{·}CH_2\text{·}CO\text{·}NHPh$$

$$+ C_6H_6 + AlCl_3 \longrightarrow CH_3\text{·}CO\text{·}CH_2\text{·}COPh$$
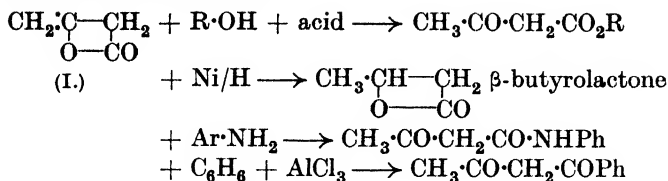
The Peroxide Effect.

Since last year's Report,[57] work on the now widely recognised effects of oxygen and peroxides on organic reactions has been continued by Kharasch, Mayo, and their collaborators at Chicago, and a comprehensive review has appeared.[58]

Although in no case has any effect of oxygen or peroxides on the *orientation* of addition of hydrogen iodide (or chloride) been observed, it has been found by M. S. Kharasch and C. Hannum [59] that peroxides greatly accelerate the addition of hydrogen iodide to allyl bromide. This is now shown to be due to the liberation of iodine from hydrogen iodide by the peroxide. In the presence of 0·005 mole either of ascaridole (menthene peroxide) or of iodine the addition of hydrogen iodide to propylene is complete in less than 1 minute at $-80°$. Iodine thus has an enormous effect on the rate of addition of hydrogen iodide to olefins.[60]

The view that the orientation of addition of hydrogen iodide was influenced by the internal pressure of the solvent used was put forward by Ingold; it was stated that up to 24% of *n*-propyl iodide could be obtained from propylene in propane solution.[61] A careful and extensive repetition of the work has failed to detect the presence of *n*-propyl iodide in the product.[60]

It is sometimes suggested that the presence of traces of iodine in the hydrogen bromide may greatly influence its addition to an olefin. Even if this were so, it would not alter the fact that in nearly every case the presence of oxygen or peroxide is necessary before abnormal orientation can occur. F. R. Mayo and C. Walling [58, p. 375] on thermochemical grounds explain the absence of abnormal additions of hydrogen fluoride, chloride and iodide.[57, p. 226] Further results bearing on the mechanisms of the peroxide-catalysed and the metal-catalysed reactions have appeared.[62]

[57] *Ann. Reports*, 1939, **36**, 219.

[58] F. R. Mayo and C. Walling, *Chem. Reviews*, 1940, **27**, 351.

[59] *J. Amer. Chem. Soc.*, 1934, **56**, 1782.

[60] M. S. Kharasch, J. A. Norton, and F. R. Mayo, *ibid.*, 1940, **62**, 81.

[61] C. K. Ingold and (Miss) E. Ramsden, *J.*, 1931, 2746.

[62] M. Takebayashi, *Bull. Chem. Soc. Japan*, 1939, **14**, 290 ; 1940, **15**, 113, 116 ; O. Simamura, *ibid.*, 1940, **15**, 292 ; M. S. Kharasch and W. R. Haefele, *J. Amer. Chem. Soc.*, 1940, **62**, 2047 ; A. Michael and N. Weiner, *J. Org. Chem.*, 1940, **5**, 389.

The use of sulphuryl chloride in the chlorination of hydrocarbons (*e.g.*, in the preparation of benzyl and benzylidene chlorides, or *cyclo*hexyl chloride) has already been reported.[63]   It has now been shown [64] that, although sulphuryl chloride in the dark and in absence of catalysts does not attack aliphatic acids or acid chlorides, it will in presence of traces of peroxides (and in the dark) react vigorously with most aliphatic acids and acid chlorides.   The importance of the reaction lies in the fact that the usually reactive α-position is least affected.   *n*-Butyric acid yields 15% of α-, 55% of β-, and 30% of γ-chlorobutyric acid; a second chlorine atom tends to enter the chain at a point remote from the first chlorine atom. Acetic acid does not react.

If a halogen carrier such as iodine is added (in place of the peroxide), the reaction is slow, even at 70°, and the product is exclusively the α-chloro-acid or α-chloro-acid chloride.[64]

In the presence of light a photochemically catalysed *sulphonation* occurs; propionic acid and sulphuryl chloride, refluxed for 2 hours whilst illuminated with a 300 watt lamp (at 5 cm.), give a 37% yield of β-sulphopropionic acid ($HO_3S \cdot CH_2 \cdot CH_2 \cdot CO_2H$).   Again acetic acid is unreactive.

An interesting application of the use of peroxides is recorded by C. D. Hurd and W. A. Hoffman.[65]   If hydrogen bromide is added to *o*-allylphenyl acetate in the presence of peroxide the bromine adds terminally and then by elimination (apparently) of acetyl bromide chroman is formed; in the presence of quinol the hydrogen adds terminally and the final product is 2-methylcoumaran.   From the unacetylated allylphenol, only 2-methylcoumaran could be obtained in the presence or absence of peroxide, as the effect of the hydroxyl group neutralises that of the peroxide.

Chroman

2-Methylcoumaran
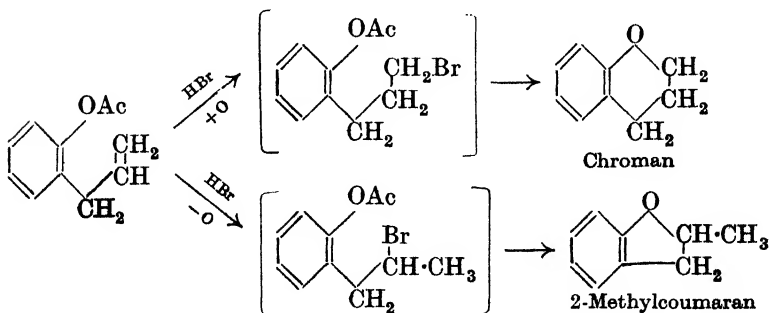
[63] *Ann. Reports*, 1939, **36**, 233.
[64] M. S. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.*, 1940, **62**, 925.
[65] *J. Org. Chem.*, 1940, **5**, 212; L. I. Smith, *Chem. Reviews*, 1940, **27**, 287.

Higher Aliphatic Compounds.

It has been possible to establish the constitution of the commoner saturated and unsaturated long-chain acids without completely freeing them from accompanying acids. But before the physical properties could be studied, methods of purification had to be improved. For the saturated compounds distillation at low temperature through a long column (electrically heated [66] or well insulated [67]) separated the homologues sufficiently for crystallisation to become effective; repeated crystallisation then removed the remaining homologues and the unsaturated impurities.[67] An account of studies on the saturated acids (and also on esters, alcohols, and paraffins) has already been given; [68] further examples of the now widely recognised polymorphism of these compounds have been reported.[69]

Unsaturated C_{18} *Acids.*—Because of their lower melting points and their instability the olefinic acids are difficult to purify. The older methods involve the rather tedious use of lead and lithium salts; in some cases success has now been achieved by the method of low-temperature crystallisation worked out by J. B. Brown and his pupils. When a dilute (5—10%) acetone solution of mixed fatty acids from natural glycerides is cooled to between $- 20°$ and $- 30°$, the saturated acids are almost completely removed; further cooling to between $- 40°$ and $- 80°$ precipitates the unsaturated acids. The apparatus and technique are simple, and should be generally applicable to the purification of low-melting substances.[70, 71]

Oleic acid (cis-$CH_3 \cdot [CH_2]_7 \cdot CH{:}CH[CH_2]_7 \cdot CO_2H$). The most persistent impurity in oleic acid is not palmitic but stearic acid, which also has 18 carbon atoms. Crystallisation at $- 20°$ to $- 25°$, however, gives a sharp separation from the saturated acids.[72, 71]

In the binary systems oleic–palmitic and oleic–stearic acids the eutectics occur at 95 and 98% of oleic acid respectively. As 1% of stearic acid lowers the melting point of oleic acid by only $0 \cdot 13°$, the

[66] E. Jantzen and C. Tiedcke, *J. pr. Chem.*, 1930, **127**, 277.

[67] J. C. Smith, *J.*, 1931, 802.

[68] *Ann. Reports*, 1938, **35**, 251.

[69] Acids and esters : F. Francis and S. H. Piper, *J. Amer. Chem. Soc.*, 1939, **61**, 577; J. B. Guy and J. C. Smith, *J.*, 1939, 615; P. E. Verkade and J. Coops, *Biochem. Z.*, 1929, **206**, 468. Acetates and ethyl esters : R. van Bellinghen, *Bull. Soc. chim. Belg.*, 1938, **47**, 640. Alcohols : K. Higasi and M. Kimbo, *Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1939, **36**, 286. Glycerides : M. G. R. Carter and T. Malkin, *J.*, 1939, 1518. *p*-Alkoxycinnamic acids : G. M. Bennett and Brynmor Jones, *J.*, 1939, 420.

[70] J. B. Brown and G. G. Stoner, *J. Amer. Chem. Soc.*, 1937, **59**, 3.

[71] J. C. Smith, *J.*, 1939, 974.

[72] J. B. Brown and G. Y. Shinowara, *J. Amer. Chem. Soc.*, 1937, **59**, 6.

inadequacy of melting points taken in capillary tubes should be evident. Pure oleic acid [71, 72, 73] has $n_D^{20°}$ 1·4597 and melts at 13·36° or 16·25° ± 0·04° (dimorphous), slowly oxidising in the air.

Elaidic acid. This *trans*-isomeride of oleic acid is even more difficult to free from stearic acid; it has consequently been made from the purest oleic acid, and the binary systems elaidic–palmitic and elaidic–stearic acid are recorded. An X-ray spacing of 48·95 A. for pure elaidic acid corresponds to a double molecule with a vertical chain (the longest spacing observed for stearic acid is 46·2 A.).[71]

Linoleic acid ($\Delta^{9:12}$-*octadecadienoic acid*).[74] J. B. Brown and J. Frankel [75] have shown that the α-linoleic acid, m. p. — 6·8°, isolated from corn oil by conversion into the tetrabromide, followed by de-bromination with zinc,[76] is identical with the main acid obtained by low-temperature crystallisation from acetone. In this case the bromination–debromination procedure does not cause a shift of the double bonds, and it actually yields a purer product than does the crystallisation process.

The isomerism of the linoleic acids is not yet worked out. Linoleic acid from natural sources is probably *cis-cis*; elaidinisation with oxides of nitrogen or with selenium yields a solid acid (m. p. 28—29°) and also a liquid acid which has not yet been purified.[77] Linoleic acid, which appears to be essential for the diet of animals, contains one $:CH·CH_2·CH:$ unit.[78]

Linolenic acid ($\Delta^{9:12:15}$-*octadecatrienoic acid*). This has been obtained in 83—88% purity, by crystallisation first from acetone and then from light petroleum, of the acids of linseed or perilla oil. The specimen melted at — 11·5°. In this case the acid obtained by bromination–debromination seems different from that obtained by crystallisation.[79] T. Moore [80] has shown that prolonged heating of linseed oil during saponification causes conjugation of the double bonds. The acid formed (m. p. 77—79°) is named ψ-elæostearic acid because of the similarity of its absorption band to that of elæostearic acid.

[73] D. H. Wheeler and R. W. Riemenschneider, *Oil and Soap*, 1939, **16**, 207; P. J. Hartsuch, *J. Amer. Chem. Soc.*, 1939, **61**, 1142.

[74] R. D. Haworth, *J.*, 1929, 1456.

[75] *J. Amer. Chem. Soc.*, 1938, **60**, 54. Compare R. W. Riemenschneider, D. H. Wheeler, and C. E. Sando, *J. Biol. Chem.*, 1939, **127**, 391.

[76] A. Rollett, *Z. physiol. Chem.*, 1909, **62**, 410.

[77] J. P. Kass and G. O. Burr, *J. Amer. Chem. Soc.*, 1939, **61**, 1062.

[78] E. M. Hume, L. C. A. Nunn, I. Smedley-Maclean, and H. A. Smith, *Biochem. J.*, 1938, **32**, 2162.

[79] G. Y. Shinowara and J. B. Brown, *J. Amer. Chem. Soc.*, 1938, **60**, 2734; J. W. McCutcheon, *Canadian J. Res.*, 1940, **18 B**, 231.

[80] *Biochem. J.*, 1937, **31**, 142; J. P. Kass and G. O. Burr, *J. Amer. Chem. Soc.*, 1939, **61**, 3292.

Linoleyl and linolenyl alcohols can be prepared by reduction of the corresponding esters with sodium in ethyl alcohol; use of butyl alcohol brings about conjugation of the double bonds.[81]

Ricinoleic acid. Castor oil is a mixture of several glycerides and the acid obtained by hydrolysis contains 80—86% of ricinoleic acid, 12-hydroxy-*cis*-Δ^9-octadecenoic acid,

$$CH_3 \cdot [CH_2]_5 \cdot CH(OH) \cdot CH_2 \cdot CH\!:\!CH \cdot [CH_2]_7 \cdot CO_2H$$

Although many preparations are described, it is unlikely that the acid has ever been obtained pure. By low-temperature crystallisation ($-50°$ and $-65°$) J. B. Brown and (Miss) N. D. Green [82] prepared methyl ricinoleate of above 99% purity, but hydrolysis of this with hot alkali caused dehydration and polymerisation. Partial hydrolysis at 0—$4°$, followed by low-temperature crystallisation, gave an acid of m. p. $5.5°$ and approximately 96% purity.

A new series of oxidation experiments [83] shows that both ricinoleic acid and its *trans*-isomeride, ricinelaidic acid, yield mixtures of trihydroxystearic acids (m. p. $110°$ and $141°$). These trihydroxyacids on oxidation with periodic acid yield β-hydroxypelargonic aldehyde, $CH_3 \cdot [CH_2]_5 \cdot CH(OH) \cdot CH_2 \cdot CHO$ and aldehydoazelaic acid, $CHO \cdot [CH_2]_7 \cdot CO_2H$, confirming the accepted structure of ricinoleic and ricinelaidic acids.

In a comprehensive study of the thermal decompositions of (crude) castor oil by A. Barbot [84] conditions are indicated for obtaining maximum yields of heptaldehyde and Δ^{10}-undecenoic acid (500 g. of oil give 115 g. of aldehyde and 66 g. of acid). The bulky residue from the thermal decomposition has received a good deal of attention. Barbot notes that dehydration of the ricinoleic acid to $\Delta^{9:11}$- and $\Delta^{9:12}$-octadecadienoic acids precedes the polymerisation, and suggests that the residue is largely formed by a Diels addition of the $\Delta^{9:11}$-acid to the other unsaturated acids. The tetrahydrobenzene derivatives with long side chains thus formed immediately change to benzene derivatives, the hydrogen atoms reducing some of the side chain double bonds. In support of this view he claims to have obtained from the residue (by nitration and reduction) a diazotisable amine.

From the examples already given it is evident that good progress has been made in the isolation and purification of the octadecenoic acids. That they should be obtained 100% pure is of special importance in biochemical studies; by modification of the existing

[81] J. P. Kass and G. O. Burr, *J. Amer. Chem. Soc.*, 1940, **62**, 1796.

[82] *Ibid.*, p. 738.

[83] St. E. Brady, *ibid.*, 1939, **61**, 3464. Compare J. T. Scanlan and D. Swern, *ibid.*, 1940, **62**, 2305, 2309.

[84] *Ann. Chim.*, 1939, **11**, 519. This paper contains a full bibliography.

methods (low-temperature crystallisation, fractional distillation of esters, lead, mercury and lithium salt separation, bromination–debromination) and by use of chromatographic absorption [85] homogeneous products should eventually be obtained.

Elæostearic acid ($\Delta^{9:11:13}$-*octadecatrienoic acid*). The α-form (m. p. 49°) of this acid is the chief acid of tung oil, which is used as a " drying " oil. On standing or on irradiation with ultra-violet light it changes to a β-form (m. p. 72°). The two forms give different addition products with maleic anhydride.[86, 87] The molecular refraction and the parachor have been determined with specially purified specimens.[88]

Punicic and trichosanic acids. Although the isolation of several isomerides of elæostearic acid has been reported, usually the substances have been insufficiently characterised. Pomegranate seed (*Punica granatum*) yields an acid, punicic acid,[89] which has a high exaltation of molecular refraction (6·9 units), and is reducible (6 atoms of hydrogen) to stearic acid. It is oxidised to *n*-valeric, oxalic and azelaic acids (the methyl ester yields methyl azelate); it isomerises to β-elæostearic acid, identified as the maleic anhydride derivative; it depresses the melting point of the α- or β-elæostearic acids to a point below the eutectic of the α-β-system. Finally, *X*-ray analysis shows it to be distinct, and not merely a mixture of α- and β-elæostearic acids.[89, 90] The isolation of a fourth isomeride, trichosanic acid (m. p. 35°), from the seeds of *Trichosanthes curcumeroides* is claimed.[89]

Parinaric acid. The first conjugated acid of the tetraene series is parinaric acid from the kernels of *Parinarium laurinum*. This acid, which crystallises in large plates, m. p. 83·5°, and oxidises rapidly in the air, was at first regarded by M. Tsujimoto and H. Koyanagi[91] as a triene. Later it was shown to absorb four molecular proportions of hydrogen to yield stearic acid.[92] Oxidation with permanganate yielded azelaic, propionic, and oxalic acids, all carefully identified.[92] Four structures fit these facts; E. H. Farmer and E. Sutherland[92] prefer $CH_3 \cdot CH_2 \cdot [CH\vcentcolon CH]_4 \cdot [CH_2]_7 \cdot CO_2H$, as it contains the widely occurring system, $\vcentcolon CH \cdot [CH_2]_7 \cdot CO_2H$.

[85] C. Manunta, *Helv. Chim. Acta*, 1939, **22**, 1156.

[86] R. S. Morrell and H. Samuels, *J.*, 1932, 2251; H. P. Kaufmann and J. Baltes, *Fette und Seifen*, 1936, **43**, 93.

[87] E. H. Farmer and E. S. Paice, *J.*, 1935, 1630.

[88] S. W. Wan and M. C. Chen, *J. Amer. Chem. Soc.*, 1939, **61**, 2283.

[89] Y. Toyama and T. Tsuchiya, *J. Soc. Chem. Ind. Japan*, 1935, **38**, 182 B; Y. Toyama and K. Vozaki, *ibid.*, 1937, **40**, 249 B.

[90] E. H. Farmer and F. A. Van den Heuvel, *J.*, 1936, 1809.

[91] *J. Soc. Chem. Ind. Japan*, 1933, **36**, 110, 673 B.

[92] *J.*, 1935, 759.

Licanic acid.   Another unusual type of acid is licanic acid, from Brazilian oiticica oil.   It was originally thought [93] to be an isomeride of elæostearic acid.   W. B. Brown and E. H. Farmer [94] found that it was reduced catalytically to hexahydrolicanic acid, which proved to be a ketostearic acid.   Chromic acid oxidation of this keto-acid gave succinic and probably myristic acid, $CH_3 \cdot [CH_2]_{12} \cdot CO_2H$, which indicate a γ-ketostearic acid.   The hexahydrolicanic acid was then found [94] to be identical with a specimen of synthetic γ-ketostearic acid.[95]   On permanganate oxidation licanic acid yields valeric acid and γ-ketoazelaic acid.   From these facts licanic acid is seen to be 4-keto-$\Delta^{9 \,:\, 11 \,:\, 13}$-octadecatrienoic acid (m. p. 74—75°).   During the commercial preparation of oiticica oil the licanic acid is partly converted by the heat treatment into an *iso*-acid, probably a geometrical isomeride.[94]

Higher Unsaturated Acids.—Arachidonic acid ($C_{20}H_{32}O_2$).   This acid, which is obtained from the phosphatides of ox suprarenals, has been reduced to arachidic acid (eicosanoic acid, $C_{20}H_{40}O_2$); the normal iodine number shows that the four double bonds are not conjugated.[96]

By fractional crystallisation from acetone of the methyl esters of the mixed acids, methyl arachidonate (liquid even at $-80°$) is left in the filtrate.   It is obtained in 75% purity by evaporation; if the product is fractionally distilled or subjected to the bromination-debromination process, the purity (as estimated by iodine or bromine number) reaches 90—100%.[97]

Neither carbon dioxide nor oxalic acid is produced by ozonolysis or by oxidation with permanganate in acetone solution, and the absence of the $\vdots CH \cdot CH_2 \cdot CH \vdots$ unit is inferred.   From the identification among the oxidation products of acetaldehyde, succinic and adipic acids the authors tentatively suggest that arachidonic acid is $\Delta^{6 \,:\, 10 \,:\, 14 \,:\, 18}$-eicosatetraenoic acid.[97]

Preliminary results of another investigation [98] suggest a different formula.   Arachidonic acid purified by the bromination-debromination process and oxidised with aqueous alkaline permanganate certainly gave oxalic acid; valeric and hexoic, succinic and glutaric acids were probably present.   As the $\vdots CH \cdot CH_2 \cdot CH \vdots$ unit is not excluded, and because of the biosyntheses of arachidonic

[93] J. Van Loon and A. Steger, *Rec. Trav. chim.*, 1931, **50**, 936.
[94] *Biochem. J.*, 1935, **29**, 631.
[95] P. W. Clutterbuck and R. Raper, *ibid.*, 1925, **19**, 385.
[96] A. W. Bosworth and E. W. Sisson, *J. Biol. Chem.*, 1934, **107**, 489.
[97] G. Y. Shinowara and J. B. Brown, *ibid.*, 1940, **134**, 331.
[98] D. E. Dolby, L. C. A. Nunn, and I. Smedley-Maclean, *Biochem. J.*, 1940, **34**, 1422.

from linoleic acid,[99] it is suggested that arachidonic is $\Delta^{5:8:11:14}$-eicosatetraenoic acid :

$CH_3 \cdot [CH_2]_4 \cdot CH{:}CH \cdot CH_2 \cdot CH{:}CH \cdot [CH_2]_7 \cdot CO_2H,$ linoleic   acid ; $CH_3 \cdot [CH_2]_4 \cdot CH{:}CH \cdot CH_2 \cdot CH{:}[CH \cdot CH_2 \cdot CH]_2 {:} CH \cdot [CH_2]_3 \cdot CO_2H,$ arachidonic acid.

These divergent results cannot be reconciled even by making allowance for the different courses which oxidations with permanganate may take under different conditions.[1, 74]

Docosahexaenoic acid ($C_{22}H_{32}O_2$).   Many highly unsaturated acids have been reported to occur in the fish oils, but in most cases it is doubtful whether the acids are homogeneous; the wider application of a recent advance in technique seems likely to clarify the position. E. H. Farmer and F. A. Van den Heuvel [2] have subjected to molecular distillation the mixed methyl esters from fish oils (after preliminary removal of the more saturated acids).   This distillation involves heating a film of the ester for only 15 seconds to temperatures below 100° at a pressure of 10^{-4} mm. or lower, and condensation of the vapour on a cold surface separated from the heated film by less than the mean free path of the molecules.   The authors point out that the degree of separation of oleic and erucic acids (C_{18} and C_{22}) should be 3·5 times as great at 60° as at 264° and calculate that at a given temperature the relative number of molecules of various acids distilling from an equimolecular mixture will be :

acids	C_{16}	C_{18}	C_{20}	C_{22}
molecules	100	21·5	4·2	0·85

Such a procedure separates the acids (or esters) sharply according to chain length, and the yields are high : hundreds of grams of these fractions now become available.   The C_{16}, C_{18}, and C_{20} acid fractions each contain acids of different degrees of unsaturation, but the C_{22} fraction is homogeneous docosahexaenoic acid, and attention has been concentrated on this.   The molecular refraction shows that there is no conjugation of the double bonds.   Ozonisation of the acid gave acetaldehyde, acetic acid, carbon dioxide and succinic acid; the methyl ester on oxidation gave, besides these, methyl hydrogen succinate.   No formaldehyde or oxalic acid was detected.   It follows that the end groups are $CH_3 \cdot CH{:}$ and ${:}CH \cdot CH_2 \cdot CH_2 \cdot CO_2H$ (or ${:}CH \cdot CH_2 \cdot CH_2 \cdot CO_2Me$) and that four ${:}CH \cdot CH_2 \cdot CH{:}$ units are interpolated in some way not yet determined ; five structures are possible (omitting *cis*- and *trans*-forms).

There was no sign of " clupanodonic acid " ($C_{22}H_{34}O_2$), isolated

[99] L. C. A. Nunn and I. Smedley-Maclean, *Biochem. J.*, 1938, **32**, 2178.

[1] A. Lapworth and E. N. Mottram, *J.*, 1925, **127**, 1987.

[2] *J. Soc. Chem. Ind.*. 1938, **57**, 24 ; *J.*, 1938, 427.

by the older methods in very small yield from Japanese sardine oil,[3] and there was good reason to believe that other docosapentaenoic acids were absent. Farmer and Van den Heuvel[2] find that the hydrogen value/refractivity relationship is a straight line for fractions obtained by molecular distillation (up to the C_{22} acid), but that the products of ordinary distillation (0·1—5 mm.) and clupanodonic acid do not fall on this line. The heat treatment has caused the loss of a double bond; it is difficult to avoid the conclusion that much of the earlier work on the highly unsaturated acids is in need of revision.

Higher Saturated Acids. Biosynthesis.—Support for the view that fatty acids in Nature are synthesised from sugars comes from the observation that an increase in fat content is often accompanied by a decrease in sugar. That the synthesis was *via* direct union of hexoses seemed to be supported by the widespread occurrence of acids with 12, 18, 24 and 30 carbon atoms.[4] In the last few years, however, it has become obvious that fatty acids occur in a more evenly graded sequence than was formerly supposed and theories of synthesis by addition of 2 carbon atoms at a time, from acetaldehyde or pyruvic acid, are now more favoured.[5] Lignoceric and cerebronic acids were hitherto regarded as having 24 carbon atoms, and the disproof of this view is worth discussing at length.

The cerebrosides of the brain are usually divided into phrenosin and kerasin. Phrenosin on hydrolysis yields galactose, sphingosin ($C_{18}H_{37}O_2N$) and cerebronic (phrenosinic) acid; kerasin similarly affords galactose, sphingosin and lignoceric acid.[6] Lignoceric acid, which has approximately the composition $C_{24}H_{48}O_2$, is obtained also from beech-wood tar and peanut oil; its history, like that of cerebronic acid, is very confused and only the recent work can usefully be reported. By careful fractional distillation of lignoceric esters from peanut oil E. Jantzen and C. Tiedcke[66] obtained *n*-eicosanoic, docosanoic and tetracosanoic acids, and a residue of higher acids. F. Francis, S. H. Piper, and T. Malkin[7] showed by *X*-ray analysis of the crystals that the acid from beech-wood tar was mainly *n*-tetracosanoic acid and that branched-chain acids were absent. Kerasin was carefully purified by A. C. Chibnall, S. H. Piper, and E. F. Williams,[8] and when the lignoceric acid from it was examined by *X*-ray methods it was found to be a mixture

[3] M. Tsujimoto, *J. Soc. Chem. Ind. Japan*, 1920, **23,** 1007.

[4] E. Fischer, " Untersuchungen über Kohlenhydrate und Fermenten," Berlin, 1909, p. 110.

[5] I. Smedley-Maclean, *Ergebn. Enzymforsch.*, 1936, **5,** 285 (a review).

[6] *Ann. Reports*, 1929, **26,** 223.

[7] *Proc. Roy. Soc.*, 1930, *A*, **128,** 242.

[8] *Biochem. J.*, 1936, **30,** 100.

of approximately 10% of C_{22}, 80% of C_{24}, and 10% of C_{26} acids; there must therefore be at least three kerasins.

There was a prolonged controversy between A. Klenk and P. A. Levene over the constitution of cerebronic acid. Klenk considered that cerebronic acid was α-hydroxytetracosanoic acid, since on oxidation (with chromic acid) it yielded tricosanoic acid. According to Levene the oxidation product was tetracosanoic acid, and cerebronic acid was therefore α-hydroxypentacosanoic acid.[9] In 1929 [10] and again in 1933 [11] Levene stated that the cerebronic acid was really a mixture of acids. Klenk disagreed with this view and claimed an 85% yield of pure tricosanoic acid on oxidation of cerebronic acid.[12] Since the confusion seemed in part to be due to difficulty in identifying the oxidation products, tricosanoic and tetracosanoic acids were prepared [13] from pure undecoic and dodecoic acids respectively by the Robinson synthesis.[14]

From the binary system tricosanoic–tetracosanoic acid it was evident that the identification of the acids by melting points in capillary tubes would be unsatisfactory, there being less than $0\cdot5°$ difference in melting point between mixtures containing from 0 to 40% of tetracosanoic acid. A small amount of the oxidation product supplied by Professor Klenk was tested by a micro melting-point method and appeared to melt slightly below any point in the C_{23}–C_{24} system.[13] (Miss) D. M. Crowfoot [15] examined the synthetic acids and the oxidation product by X-ray methods and concluded that the oxidation product was mainly tricosanoic acid, mixed probably with pentacosanoic acid.

In the meantime cerebronic acid (from highly purified phrenosin) and its oxidation product were prepared by A. C. Chibnall, S. H. Piper, and E. F. Williams.[8] After a comprehensive examination by mixed melting-point and by X-ray methods they concluded that the oxidation product was a mixture of C_{21}, C_{23}, and C_{25} acids and therefore that cerebronic acid was a mixture of α-hydroxy-docosanoic, -tetracosanoic and -hexacosanoic acids. It is now obvious that the composition of cerebronic acid and of the oxidation product will depend on the purification to which they are subjected : recrystallisation will reduce the proportion of the shorter-chain acids.

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[9] *Ann. Reports*, 1929, **26**, 224.

[10] F. A. Taylor and P. A. Levene, *J. Biol. Chem.*, 1929, **84**, 23.

[11] *Idem, ibid.*, 1933, **102**, 535.

[12] E. Klenk and W. Diebold, *Z. physiol. Chem.*, 1933, **215**, 79.

[13] R. Ashton, R. Robinson, and J. C. Smith, *J.*, 1936, 283.

[14] (Mrs.) G. M. Robinson and R. Robinson, *J.*, 1925, **127**, 175; (Mrs.) G. M. Robinson, *J.*, 1930, 745; *Ann. Reports*, 1938, **35**, 251.

[15] *J.*, 1936, 716.

Cerebronic acid (d-) melts at $100 \cdot 5$—$101°$,[16] or at $102 \cdot 3$—$102 \cdot 6°$, with $[\alpha]_D^{22°} + 3 \cdot 33°$.[8, 13]   Synthetic ($dl$)-$\alpha$-hydroxytetracosanoic acid,[13, 17] melts at $99 \cdot 7°$, and synthetic l-α-hydroxytetracosanoic acid at $99°$, with $[\alpha]_D^{22°} - 3 \cdot 13°$.[17]   The significance of these melting-point differences is not clear, and unfortunately crystals of the α-hydroxy-acid suitable for determination of the chain length by X-ray methods have not yet been obtained.   Chibnall's analytical figures for cerebronic acid indicate an average composition of $C_{25}H_{50}O_3$ and the X-ray measurements on the oxidation products make it almost certain that cerebronic acid is a mixture of α-hydroxy-docosanoic, -tetracosanoic, and -hexacosanoic acids.*

When these results are considered in the light of recent work on waxes, it would appear exceptional if lignoceric and cerebronic acids were homogeneous compounds.

In a most important series of papers, which unfortunately cannot be fully reviewed here, Chibnall, Piper and their collaborators examined about twenty plant and insect waxes.[19]   They developed methods for the isolation of the acids, primary and secondary alcohols, ketones and paraffins.[20]   A great number of these compounds were also synthesised as standards,[21] and the binary and ternary systems were examined by a special melting-point technique.[22]   Another feature of the work was the application of X-ray analysis to films of the pure substances and of mixtures of homologues.   Most of the leaf waxes consisted principally of primary alcohols, with lesser amounts of fatty acids, paraffins and secondary alcohols, but tobacco leaf wax is made up exclusively of

[16] E. Klenk and L. Clarenz, Z. physiol. Chem., 1939, 257, 268.

[17] A. Müller and I. Binzer, Ber., 1939, 72, 615.

[18] H. Mendel and J. Coops, Rec. Trav. chim., 1939, 58, 1133.

[19] Summarising papers : A. C. Chibnall, S. H. Piper, A. Pollard, E. F. Williams, and P. N. Sahai, Biochem. J., 1934, 28, 2189; A. C. Chibnall and S. H. Piper, ibid., p. 2209.

[20] A. C. Chibnall, S. H. Piper, A. Pollard, J. A. B. Smith, and E. F. Williams, ibid., 1931, 25, 2095.

[21] S. H. Piper, A. C. Chibnall, and E. F. Williams, ibid., 1934, 28, 2175.

[22] S. H. Piper, A. C. Chibnall, S. J. Hopkins, A. Pollard, J. A. B. Smith, and E. F. Williams, ibid., 1931, 25, 2072; Ann. Reports, 1938, 35, 260.

* In Klenk's latest paper [16] cerebronic acid is oxidised with lead tetra-acetate, and the resulting aldehyde converted via the oxime and nitrile into an acid, m. p. $77 \cdot 7$—$78 \cdot 1°$.   If this is a melting point in a capillary tube, it is 1—2° lower than the value for synthetic tricosanoic acid.

A very useful method of degrading a fatty acid to the next lower homologue via the α-hydroxy-acid (which is oxidised with lead tetra-acetate and oxygen in 89% yield) has been carefully worked out.[18]   Despite the six stages involved the process is said to give an 84% yield of pure pentadecoic acid from palmitic acid.

paraffins.[19]   The insect waxes vary from cochineal wax (from which triacontanoic acid, 15-keto-n-tetratriacontanol and 13-keto-n-dotriacontanoic acid were isolated [23]) to beeswax, which yielded the 24, 26, 28, 30, 32, and 34 carbon acids, the primary alcohols C_{24} to C_{34}, and the paraffins $C_{25. 27. 29. 31}$.[19]   These researches have swept away many conflicting views previously held on the waxes; they have definitely established that all the acids and primary alcohols have an even number of carbon atoms * and that all the paraffins are odd-numbered.   Most of the wax acids and wax alcohols formerly regarded as single substances have been shown to be mixtures of homologues.

Assuming that the saturated acids, ketonic acids, and hydroxy-acids are formed from unsaturated acids synthesised from shorter units, Chibnall and Piper [19] discuss in detail the metabolism of waxes.   They suggest that the saturated acid, by direct reduction, gives the primary alcohol; β-oxidation of the acid gives a keto-acid, which then yields either the next lower even-numbered acid, or, by loss of carbon dioxide, a methyl ketone.   Reduction of this ketone then gives an *odd*-numbered paraffin :

$$R \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot OH \longleftarrow R \cdot CH_2 \cdot CH_2 \cdot CO_2H$$
$$\downarrow$$
$$R \cdot CO \cdot CH_2 \cdot CO_2H \longrightarrow R \cdot CO \cdot CH_3$$
$$\downarrow \qquad\qquad\qquad \downarrow$$
$$R \cdot CH_2 \cdot OH \longleftarrow R \cdot CO_2H \qquad\qquad R \cdot CH_2 \cdot CH_3$$
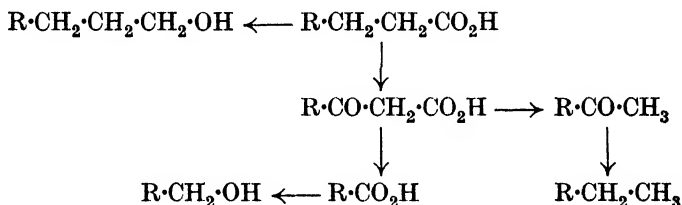
The interesting ω-hydroxy-acids ($OH \cdot CH_2 \cdot [CH_2]_{10} \cdot CO_2H$, sabinic; $OH \cdot CH_2 \cdot [CH_2]_{14} \cdot CO_2H$, juniperic; and
$$OH \cdot CH_2 \cdot [CH_2]_7 \cdot CH \colon CH \cdot [CH_2]_5 \cdot CO_2H,$$
ambrettolic) are considered by Chibnall and Piper [19] as hydroxylated products of unsaturated acids such as Δ^9-decenoic [24] (in this case the addition of water to the double bond would have to be abnormally oriented).

Alternatively these authors suggest that the hydroxy-acids arise

[23] A. C. Chibnall, A. L. Latner, E. F. Williams, and C. A. Ayre, *Biochem. J.*, 1934, **28**, 313.

[24] A. Grün and T. Wirth, *Ber.*, 1922, **55**, 2197.

* No long-chain n-fatty acid with an odd number of carbon atoms has yet been found in Nature.   Probably the most convincing claim to have isolated " daturic " acid (margaric, heptadecyclic acid, from thorn apple seeds) was made by H. Meyer and R. Beer (*Monatsh.*, 1912, **33**, 311), but this was completely disproved by P. E. Verkade and J. Coops, jun. (*Biochem. Z.*, 1929, **206**, 468).

by the ω-oxidation [25] of n-fatty acids; palmitic acid would yield thapsic, and this on reduction, juniperic acid: $CH_3 \cdot [CH_2]_{14} \cdot CO_2H \longrightarrow HO_2C \cdot [CH_2]_{14} \cdot CO_2H \longrightarrow OH \cdot CH_2 \cdot [CH_2]_{14} \cdot CO_2H$.

A different view is taken by P. C. Mitter and P. N. Bagchi,[26] who consider that these acids are derived from terpenes (which sometimes occur in the same oil). Farnesol, by reduction of the double bonds, removal of the side-chain methyl groups, and oxidation of the terminal methyl, would yield sabinic acid:

$$CH_3 \cdot CMe\dot{:}CH \cdot CH_2 \cdot CH_2 \cdot CMe\dot{:}CH \cdot CH_2 \cdot CH_2 \cdot CMe\dot{:}CH \cdot CH_2 \cdot OH$$

$$\downarrow$$

$$CO_2H \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot OH$$
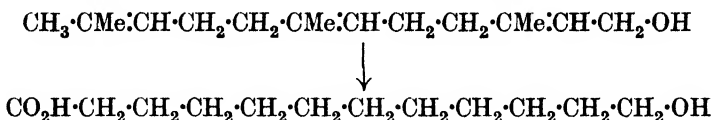
Similarly a hypothetical diterpene alcohol would yield juniperic acid.

R. Kuhn,[27] making use of the reactivity of the methyl group in crotonaldehyde,[28] condensed crotonaldehyde with itself in presence of piperidine acetate, and obtained a series of polyene aldehydes:

$$2CH_3 \cdot CH\dot{:}CH \cdot CHO \longrightarrow CH_3 \cdot [CH\dot{:}CH]_3 \cdot CHO$$
$$2CH_3 \cdot [CH\dot{:}CH]_3 \cdot CHO \longrightarrow CH_3 \cdot [CH\dot{:}CH]_7 \cdot CHO$$
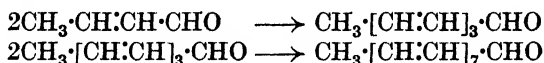
The hexadecaheptaenal on catalytic reduction gave hexadecyl (cetyl) alcohol; condensation with malonic acid gave hexadecaheptaenylidenemalonic acid (deep violet), which on decarboxylation and catalytic reduction yielded stearic acid.

These syntheses indicate one way in which fatty acids and alcohols may be built up in Nature from acetaldehyde, crotonaldehyde or pyruvic acid. According to Kuhn, reduction in Nature would have to occur at an early stage, since highly unsaturated acids with conjugated double bonds would be coloured, and these colours have not yet been observed in the fats of plants or animals. It is interesting to speculate on the way in which various unsaturated acids could arise from Kuhn's polyene acids, but recent work has shown that in animals (if not in plants) the fatty acids can be interconverted with great ease. When esters of acids containing deuterium are fed to rats, the metabolism of the acids can be investigated by estimating the deuterium content of the

[25] P. E. Verkade and J. Van der Lee, *Biochem. J.*, 1934, **28**, 31; P. E. Verkade, *Chem. and Ind.*, 1938, **16**, 704.

[26] *J. Indian Chem. Soc.*, 1939, **16**, 402. Compare R. Kuhn, F. Köhler, and L. Köhler, *Z. physiol. Chem.*, 1936, **242**, 171.

[27] Pedler Lecture, *J.*, 1938, 608. Compare K. S. Raper, *J.*, 1907, **91**, 1831.

[28] A. Lapworth, *J.*, 1901, **79**, 1273; I. Smedley, *J.*, 1911, **99**, 1627.

acids isolated, after a lapse of time, from various parts of the body.[29]   The following changes have been shown to occur :

$$\underset{\text{Stearic}}{CH_3 \cdot [CH_2]_{16} \cdot CO_2H} \quad \rightleftharpoons \quad \underset{\text{Palmitic}}{CH_3 \cdot [CH_2]_{14} \cdot CO_2H} \quad \longrightarrow \quad \underset{\text{Myristic}}{CH_3 \cdot [CH_2]_{12} \cdot CO_2H}$$

$$\updownarrow \qquad\qquad\qquad \updownarrow$$

$$\underset{\text{Oleic}}{CH_3 \cdot [CH_2]_7 \cdot CH:CH \cdot [CH_2]_7 \cdot CO_2H} \quad \underset{\text{Palmitoleic}}{CH_3 \cdot [CH_2]_5 \cdot CH:CH \cdot [CH_2]_7 \cdot CO_2H}$$

<div align="right">T. H.
J. C. S.</div>
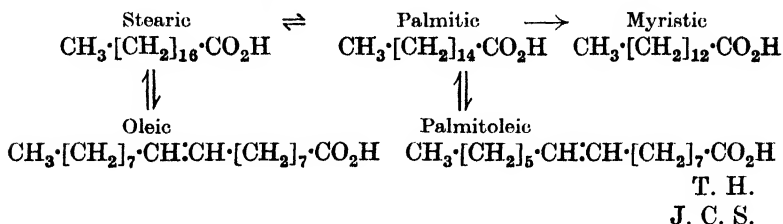
Traumatic Acid.—It has long been recognised that there are formed or liberated at the injured surfaces of plant tissues, water-soluble substances which are capable of promoting renewed growth activity in mature uninjured cells or tissues; such substances are called wound-hormones.

The isolation of a wound-hormone from the aqueous extract of ground bean-pods has been reported,[30] and the constitution of this substance, now called traumatic acid, determined.[31]   Analysis and molecular weight determinations gave the formula $C_{12}H_{22}O_4$, and an equivalent weight determination by direct titration gave a value of 118, corresponding to a dibasic acid.   Catalytic hydrogenation furnished decane-1 : 10-dicarboxylic acid, identified by its melting point and its mixed melting point with a synthetic specimen.[32]

Oxidation of traumatic acid with permanganate in acetone furnished sebacic acid, thus proving the αβ-position of the double bond.   Hence traumatic acid appeared to be Δ¹-decene-1 : 10-dicarboxylic acid, and this constitution was proved by synthesis.[31] Methyl undecylenate, ozonised according to the method of Noller and Adams,[33] yielded the half aldehyde-ester of sebacic acid.   This condensed readily with malonic acid in pyridine, and carbon dioxide was evolved.   Hydrolysis of the product yielded the required Δ¹-decene-1 : 10-dicarboxylic acid, identical with the natural product :

$$CH_2:CH \cdot [CH_2]_8 \cdot CO_2Me \xrightarrow{\quad O_3 \quad} CHO \cdot [CH_2]_8 \cdot CO_2Me \xrightarrow[-\,CO_2]{\quad CH_2(CO_2H)_2 \quad}$$

$$\underset{\text{Traumatic acid}}{CO_2H \cdot CH:CH \cdot [CH_2]_8 \cdot CO_2H}$$
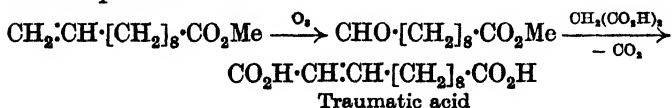
[29] D. W. Stetten and R. Schoenheimer, *J. Biol. Chem.*, 1940, **133**, 347; compare *Ann. Reports*, 1938, **35**, 346.

[30] J. English (jun.), J. Bonner, and A. J. Haagen-Smit, *Proc. Nat. Acad. Sci.*, 1939, **25**, 323.

[31] *Idem, J. Amer. Chem. Soc.*, 1939, **61**, 3434.

[32] P. Chuit, *Helv. Chim. Acta*, 1926, **9**, 264.

[33] C. R. Noller and R. Adams, *J. Amer. Chem. Soc.*, 1926, **48**, 1074.

In the course of the investigations [30, 31] a large number of organic compounds were tested for similar activity; these included indole-α-acetic acid, vitamins B_1, B_2, and B_6 and other plant growth substances, but the only active substances were certain homologues and analogues of decene-1 : 10-dicarboxylic acid. The hydrogenation product, decane-1 : 10-dicarboxylic acid, possesses approximately half the activity of traumatic acid; hence the double bond, whilst not essential, nevertheless enhances activity. The saturated dibasic acids containing 7 or fewer carbon atoms are without significant activity. On the other hand, suberic and azelaic acids with 8 and 9 carbon atoms respectively possess slight activity, and sebacic acid of 10 carbon atoms possesses half the activity of traumatic acid.

Phthioic and Tuberculostearic Acids.—In an investigation of the lipides of *B. tuberculosis*, R. J. Anderson [34] isolated two acids, which were separated by high vacuum distillation of their methyl esters.[35] Hydrolysis of the lower-boiling ester furnished tuberculostearic acid, $C_{19}H_{38}O_2$, an acid of only slight physiological activity. Hydrolysis of the higher-boiling ester, however, yielded phthioic acid, $C_{26}H_{52}O_2$, an acid of great importance, showing almost all the toxic properties of the bacillus itself.

Determination of the constitution of tuberculostearic acid (m. p. 10—11°) was undertaken by M. A. Spielman,[36] who considered it to be 10-methylstearic acid; for on oxidation with chromic acid it yielded methyl *n*-octyl ketone and azelaic acid together with a little octoic acid. Oxidative rupture of the molecule thus proceeds according to the scheme :

$$CH_3 \cdot [CH_2]_7 \cdot CHMe \cdot [CH_2]_8 \cdot CO_2H \longrightarrow$$
$$CH_3 \cdot [CH_2]_7 \cdot COMe + HO_2C \cdot [CH_2]_7 \cdot CO_2H$$
$$\downarrow$$
$$CH_3 \cdot [CH_2]_6 \cdot CO_2H$$
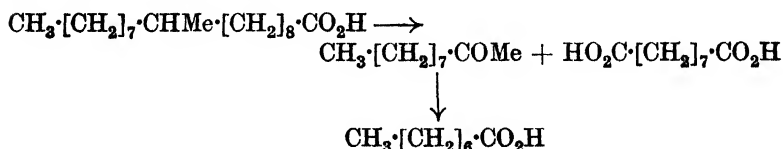
In an endeavour to prove conclusively this supposition, Spielman synthesised 10-methylstearic acid as follows : Interaction of *n*-octylmagnesium bromide (after removal of the ether) and fused zinc chloride in dry benzene provided the zinc alkyl chloride (I). Treatment of this with ω-carbethoxynonyl chloride (II) [37] gave 10-ketostearic acid (III), which was converted into its barium salt, and a stirred suspension of the latter in ether treated with methylmagnesium iodide. The 10-hydroxy-10-methylstearic acid (IV) thus

[34] *J. Biol. Chem.*, 1929, **83**, 169.

[35] R. J. Anderson and E. Chargaff, *ibid.*, 1930, **85**, 77.

[36] *Ibid.*, 1934, **106**, 87.

[37] C. R. Fordyce and J. R. Johnson, *J. Amer. Chem. Soc.*, 1933, **55**, 3368.

produced was dehydrated, the olefinic acid esterified and hydrogenated (PtO), and the resulting saturated ester saponified :

$$CH_3 \cdot [CH_2]_7 \cdot ZnCl + Cl \cdot CO \cdot [CH_2]_8 \cdot CO_2Et \longrightarrow$$
$$\quad (I.) \qquad\qquad (II.)$$

$$CH_3 \cdot [CH_2]_7 \cdot CO \cdot [CH_2]_8 \cdot CO_2H \longrightarrow CH_3 \cdot [CH_2]_7 \cdot CMe(OH) \cdot [CH_2]_8 \cdot CO_2H$$
$$\quad (III.) \qquad\qquad\qquad\qquad\qquad (IV.)$$
$$\downarrow$$
$$CH_3 \cdot [CH_2]_7 \cdot CHMe \cdot [CH_2]_8 \cdot CO_2H$$
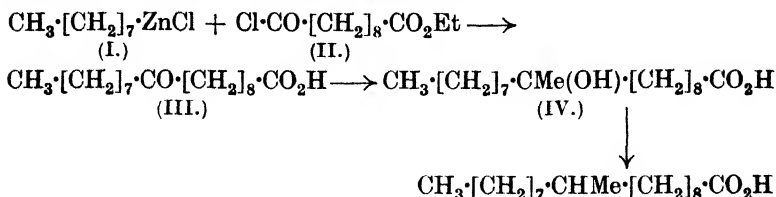
It was found, however, that this synthetic acid melted at 20—21°, whereas tuberculostearic acid melted at 10—11°, and the mixed melting point was intermediate. The melting points of the amides and of the 2 : 4 : 6-tribromoanilides, the densities and the refractive indices of the two acids agreed exactly. Spielman attributed the difference in melting point of the acids either to the presence of a trace of impurity such as 9-methylstearic acid in the natural product, or to the possibility of the natural acid being a d- or l-form (with negligible specific rotation). Resolution of the synthetic acid has not yet been reported. Owing to the interest attaching to the occurrence of branched-chain, odd-numbered acids in Nature it is unfortunate that the tuberculostearic acid has not been submitted to thorough X-ray examination.

The determination of the constitution of phthioic acid, on the other hand, has proved more difficult, and indeed the problem still awaits solution. Only a small measure of success has attended ordinary chemical methods of attack. M. A. Spielman and R. J. Anderson [38] obtained on chromic acid oxidation a small quantity of an acid, which gave analytical figures closely corresponding to $C_{11}H_{22}O_2$ but was not n-undecoic acid; indeed it was a liquid acid, and both its p-bromophenacyl ester and its 2 : 4 : 6-tribromoanilide differed greatly from those of n-undecoic acid : the conclusion was drawn that the acid must have a branched chain. E. Chargaff [39] attempted to throw light on the structure of phthioic acid by an alternative route, that of synthesising isomerides of hexacosanoic acid. By application of the malonic ester synthesis with long-chain halides, he prepared α-ethyl-n-tetracosanoic, α-n-butyl-n-docosanoic, α-n-hexyl-n-eicosanoic, α-n-octyl-n-octadecanoic, α-n-decyl-n-hexadecanoic, and α-n-dodecyl-n-tetradecanoic acids. The interesting fact emerged that introduction of an α-substituent into hexacosanoic acid (m. p. 88°) lowered its melting point by 20—30°, and since phthioic acid has a melting point of 28°, this indicates the presence of at least two branchings in the chain.

Application of surface-film measurements has strengthened this

[38] J. Biol. Chem., 1936, 112, 759.　　　[39] Ber., 1932, 65, 745.

belief. E. Stenhagen [40] carried out film measurements on some disubstituted acetic acids, and with decyldodecylacetic acid, the film collapsed at 60 A.^{2} With phthioic acid,* on the other hand, the film was much more compressed and collapsed at 38 A.^{2} This indicated to Stenhagen that in phthioic acid there was a small α-substituent which brought about a closer packing of the chains. Accordingly he expressed the opinion that the phthioic acid molecule is of the type

$$CH_3 \cdot [CH_2]_x$$
$$CH_3 \cdot [CH_2]_y \!\!\!> C \cdot CO_2H$$
$$CH_3 \cdot [CH_2]_z$$

where x and y are of the order of 12 and $z = 0$ or 1, and that the most probable formula is ethyldecyldodecylacetic acid.

The synthesis of such trisubstituted acetic acids has been attempted at Oxford.[41] Reichstein [42] has shown that trisubstituted acetic acids can be obtained by application of the Friedel–Crafts reaction with tertiary halides to methyl furoate, followed by oxidation of the furan ring :

$$\begin{array}{c} R\backslash \\ R' \!\!> CCl \\ R'' \end{array} + \begin{array}{c} \\ O \end{array} CO_2Me \longrightarrow \begin{array}{c} R\backslash \\ R' \!\!> C \\ R'' \end{array} \begin{array}{c} \\ O \end{array} CO_2Me \xrightarrow{KMnO_4} \begin{array}{c} R\backslash \\ R' \!\!> C \cdot CO_2H \\ R'' \end{array}$$
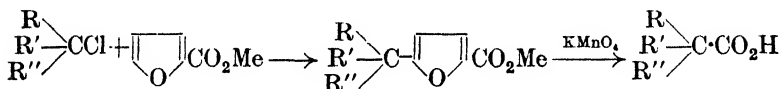
Using methyldioctylcarbinyl chloride in this procedure, there was obtained a small quantity of methyldioctylacetic acid,[41] which formed surface films similar to those of phthioic acid, and collapsing at 38 A.^{2} Further, when injected into rabbits, it produced toxic cell reactions, though these were different from those produced by phthioic acid.[41] Progress in this field has, however, been unavoidably slow owing to the great difficulties encountered in manipulating long-chain compounds with their attendant steric effects.

In the field of synthetic bactericides for the treatment of tuberculosis and the analogous pathological condition of leprosy much has been accomplished by Adams and his co-workers.[43] Adams prepared a series of di-n-alkylacetic acids and showed that, whereas maximum activity against *B. lepræ* occurred in those acids with 16 carbon atoms, they possessed only slight activity towards *B. tuberculosis*. A more potent factor against this bacterium has been prepared by Birch and Robinson.[41] Application of the Guareschi

[40] *Trans. Faraday Soc.*, 1940, **36**, 597.

[41] Sir R. Robinson, Presidential Address, *J.*, 1940, 505; A. J. Birch, D. Phil. Thesis, Oxford, 1940.

[42] T. Reichstein, H. R. Rosenberg, and R. Eberhardt, *Helv. Chim. Acta*, 1935, **18**, 721.

[43] C. R. Noller and R. Adams, *J. Amer. Chem. Soc.*, 1926, **48**, 1080, and subsequent papers; see *Ann. Reports*, 1930, **27**, 240.

* Stenhagen, unpublished result. See ref. (41).

reaction [44] to methyl n-octyl ketone led to β-methyl-β-n-octyl-glutaric acid. This dibasic acid was converted into its ester chloride, which was condensed with ethyl sodio-α-acetyl-n-heptoate, and the product hydrolysed to 5-keto-3-methyl-3-n-octyl-n-undecoic acid; Clemmensen reduction of this gave 3-methyl-3-n-octyl-n-undecoic acid :

$$n\text{-}C_8H_{17}\text{-}CH_3\text{>}CO \xrightarrow[+\ NH_3]{CN\cdot CH_2\cdot CO_2Et} C_8H_{17}\text{-}CH_3\text{>}C\text{<}^{CH_2\cdot CO_2Et}_{CH_2\cdot CO_2Et}$$

$$\xleftarrow[\dot{C}_5H_{11}]{Me\cdot CO\cdot CNa\cdot CO_2Et} C_8H_{17}\text{-}CH_3\text{>}C\text{<}^{CH_2\cdot CO_2Et}_{CH_2\cdot COCl}$$

$$\begin{array}{c}Me\\C_8H_{17}\end{array}\text{>}C\text{<}\begin{array}{l}CH_2\cdot CO_2Et\quad CO\cdot CH_3\\CH_2\cdot CO\text{---}\underset{CO_2Et}{\overset{|}{C}}\text{---}C_5H_{11}\end{array}$$

Hydrolysis ↓

$$Me\cdot[CH_2]_5\cdot CO\cdot CH_2\text{---}\underset{Me}{\overset{\overset{\displaystyle C_8H_{17}}{|}}{C}}\text{---}CH_2\cdot CO_2H \xrightarrow{Zn/Hg,HCl} Me\cdot[CH_2]_7\text{---}\underset{Me}{\overset{\overset{\displaystyle C_8H_{17}}{|}}{C}}\text{---}CH_2\cdot CO_2H$$

ββ-Di-n-octylbutyric acid
(3-Methyl-3-n-octyl-n-undecoic acid.)
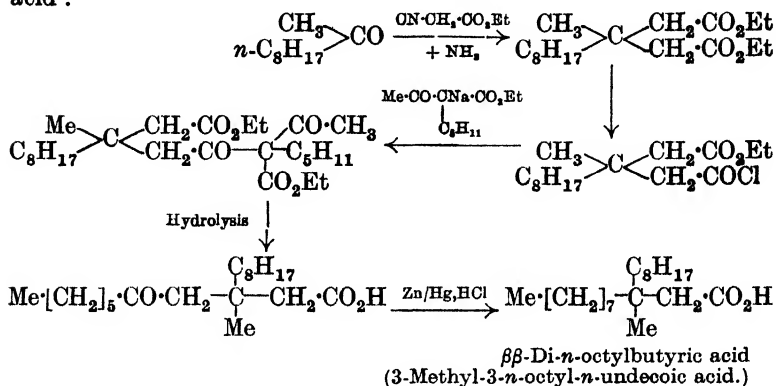
This acid, too, forms very compressed films of the phthioic acid type : it appears that the molecule in water is immersed from the carboxyl up to the branch in the chain. This fact together with the non-toxicity of the compound further indicates that phthioic acid is a trisubstituted acetic acid. When tested against *B. tuberculosis in vitro*, it has shown greater bactericidal power than any of the acids of the same molecular weight prepared by Adams.

Pantothenic Acid.—The structure of pantothenic acid has been elucidated and its synthesis completed. This acid, of which by far the richest source is liver (in which there are 40 parts per million), was first recognised as a factor capable of promoting the growth of yeast and of bacteria.[45] It has since been identified with the " chick anti-dermatitis factor " [46] and is a vitamin of importance in animal nutrition; the name has been chosen to indicate its wide occurrence. Its isolation by the original process [47] was exceedingly laborious, the vitamin being finally obtained as its calcium salt. Even in 1939 [48] the calcium salt then available gave

[44] I. Guareschi, *Atti R. Accad. Sci. Torino*, 1901, **36**, 443.

[45] R. J. Williams, C. M. Lyman, G. H. Goodyear, J. H. Truesdail, and D. Holaday, *J. Amer. Chem. Soc.*, 1933, **55**, 2912.

[46] T. Jukes, *ibid.*, 1939, **61**, 975; D. W. Woolley, H. A. Waisman, and C. A. Elvehjem, *ibid.*, p. 977.

[47] R. J. Williams, J. H. Truesdail, H. H. Weinstock, E. Rohrmann, C. M. Lyman, and C. H. McBurney, *ibid.*, 1938, **60**, 2719.

[48] R. J. Williams, H. H. Weinstock, E. Rohrmann, J. H. Truesdail, H. K. Mitchell, and C. E. Meyer, *ibid.*, 1939, **61**, 454.

an analysis indicating a formula subsequently shown to be wrong $[(C_8H_{14}O_5N)_2Ca$ instead of $(C_9H_{16}O_5N)_2Ca]$.

The determination of the structure of pantothenic acid is the outcome of a series of brilliant micro-chemical investigations. A carboxyl and at least one hydroxyl group were shown to be present, the substance did not react with nitrous acid, had no basic properties and did not evolve ammonia on hydrolysis with alkali : the $-NH_2$, the NH, and $-CO \cdot NH_2$ groups were absent, but this did not preclude the possibility of a substituted amide.[48] Hydrolysis of 3 mg. of pantothenic acid with dilute hydrochloric acid gave a fraction (0·2 mg.), b. p. 140—160°/0·06 mm., which was proved to be β-alanine hydrochloride (identified by preparation of β-naphthalenesulpho-β-alanine).[49] Attention was then focused on the " non-β-alanine " portion of the molecule, which appeared to be an α-hydroxy-lactone,[50] for after pantothenic acid had been hydrolysed with alkali (but not after hydrolysis with acid) the solution gave the ferric chloride test (clear yellow) characteristic of α-hydroxy-acids.[51]

In confirmation of this a micro-method of determining α-hydroxy-acids was applied : [50] the carbon monoxide evolved in the reaction $R \cdot CH(OH) \cdot CO_2H \xrightarrow{H_2SO_4} R \cdot CHO + CO + H_2O$ was measured, and the volume agreed well with that obtained from other α-hydroxy-acids. Further, a micro-method which had given consistent results with β-hydroxy-acids [permanganate titration of the product from the reaction $R \cdot CH(OH) \cdot CH_2 \cdot CO_2H \xrightarrow{25\% H_2SO_4} R \cdot CH{:}CH \cdot CO_2H]$ gave a zero value with pantothenic acid (and its hydrolysis product). As the hydroxy-lactone (or acid) condensed readily with aldehydes, it was assumed that a six-membered ring had been formed and therefore that the hydroxyls were in the α- and the γ-position.[50]

Still under the impression that the lactone contained five carbon atoms, Williams synthesised β-alanine derivatives of α-hydroxy-γ-n-valerolactone, α-hydroxy-β-methyl-γ-butyrolactone and α-hydroxy-α-methyl-γ-butyrolactone : these derivatives had only slight physiological activity.[50] Then came a preliminary announcement [52] that the lactone had been characterised as α-hydroxy-ββ-dimethyl-γ-butyrolactone ($C_6H_{10}O_3$ and not $C_5H_8O_3$).

In the meantime (in 1939) R. J. Williams and his co-workers had begun to co-operate with the Merck laboratories (U.S.A.).

[48] H. H. Weinstock, H. K. Mitchell, E. F. Pratt, and R. J. Williams, J. Amer. Chem. Soc., 1939, 61, 1421.

[50] H. K. Mitchell, H. H. Weinstock, E. E. Snell, S. R. Stanberry, and R. J. Williams, ibid., 1940, 62, 1776.

[51] M. A. Berg, Bull. Soc. chim., 1884, 11, 882.

[52] R. J. Williams and R. T. Major, Science, 1940, 91, 246.

The workers in these laboratories,[53] having first devised a rapid extraction of pantothenic acid from sheep's liver, began further investigations on the " lactone half." Analysis and a cryoscopic molecular weight determination indicated the formula $C_6H_{10}O_3$. Titration showed the absence of a free carboxyl group, but on heating with alkali one equivalent of alkali was consumed. Further, the rate of lactonisation indicated a γ- and not a δ-lactone ; the presence of a free hydroxyl group in the lactone was confirmed by the preparation of a monoacetate and a 3 : 5-dinitrobenzoate. A Kuhn–Roth determination of C-methyl gave a value corresponding to 26% of one C-methyl, and such a result would be expected from the presence of a *gem*-dimethyl group.

These facts suggested a formula $\overset{\displaystyle CH_2 \cdot CMe_2 {-\!\!} CH(OH) \cdot CO}{\underset{\rule{3.2cm}{0.4pt}}{\hspace{4.5cm}O}}$, which

was finally established as follows : the lactone and methylmagnesium iodide yielded a glycol, which on oxidation with lead tetraacetate gave an aldehyde, from which by the action of alkaline silver oxide a hydroxy-acid was obtained. This proved to be hydroxypivalic (β-hydroxy-$\alpha\alpha$-dimethylpropionic) acid : [53]

$$\underset{\rule{3.2cm}{0.4pt}\;O}{CH_2 \cdot CMe_2 \cdot CH(OH) \cdot CO} \longrightarrow CH_2(OH) \cdot CMe_2 \cdot CH(OH) \cdot C(OH)Me_2$$

$$\downarrow$$

$$CH_2(OH) \cdot CMe_2 \cdot CO_2H \longleftarrow CH_2(OH) \cdot CMe_2 \cdot CHO$$
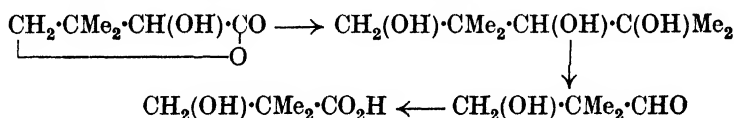
The synthesis was accomplished as follows :

$$CHMe_2 \cdot CHO + CH_2O, aq. \xrightarrow{K_2CO_3} CH_2(OH) \cdot CMe_2 \cdot CHO \xrightarrow[KCN]{NaHSO_3}$$

$$CH_2(OH) \cdot CMe_2 {-} CH \overset{OH}{\underset{CN}{{<}}} \xrightarrow[conc. HCl]{boil} \underset{\rule{3.2cm}{0.4pt}\;O}{CH_2 \cdot CMe_2 \cdot CH(OH) \cdot CO}$$

racemic lactone
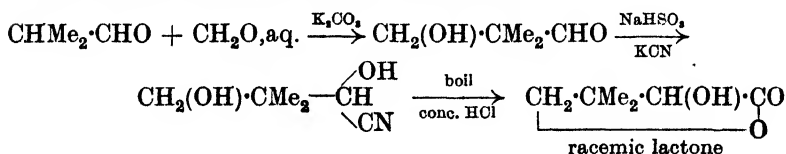
This lactone was resolved by forming the sodium salt of the acid and adding to the solution in hot water half an equivalent of quinine hydrochloride; the first crop of crystals furnished the l-form of the lactone, identical with that from pantothenic acid. By condensing the l-lactone with β-alanine ester at 70° (3 hours) and removing the ester group with cold baryta, there was obtained a pale yellow oil having all the physiological properties (and 91—97% activity) of the natural d-pantothenic acid,[54] $HO \cdot CH_2 \cdot CMe_2 \cdot CH(OH) \cdot CO \cdot NH \cdot CH_2 \cdot CH_2 \cdot CO_2H$. The calcium salt on analysis gave the correct figures, and by biological assay was

[53] E. T. Stiller, J. C. Keresztesy, and J. Finkelstein, *J. Amer. Chem. Soc.*, 1940, **62**, 1779.

[54] E. T. Stiller, S. A. Harris, J. Finkelstein, J. C. Keresztesy, and K. Folkers, *ibid.*, p. 1785.

99—100% pure. Better yields were obtained by heating the dry lactone with the dry sodium salt of β-alanine.[55] *

The only analogous compound showing activity is hydroxy-pantothenic acid,[56] $CMe(CH_2 \cdot OH)_2 \cdot CH(OH) \cdot CO \cdot NH \cdot CH_2 \cdot CH_2 \cdot CO_2H$. For the synthesis of this the necessary aldehyde $CMe(CH_2 \cdot OH)_2 \cdot CHO$ was prepared by the action of formalin on propaldehyde. Hydroxy-pantothenic acid has strong but relatively specific biological activity.

<div align="right">T. H.</div>

3. Reaction Mechanisms.

Esterification and Hydrolysis.—It was suggested in 1912 by J. Ferns and A. Lapworth [1] that, whereas the group $^-SO_2 \cdot OAlk$ reacts with fission of the O–Alk bond (*e.g.*, in alkylation by an alkyl sulphate), the corresponding bond of the ester grouping $^-CO \cdot OAlk$ normally remains intact; the points of division in the two cases are indicated by the dotted lines in the formulæ

$$^-SO_2^-O^-\!|Alk \quad \text{and} \quad ^-CO\!|^-O^-Alk$$
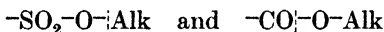
E. E. Reid [2] had already shown that the reactions of thiolbenzoic acid with ethyl alcohol and of benzoic acid with ethyl mercaptan were as follows :

$$Ph \cdot CO\!|\cdot SH + H\!|OEt \longrightarrow Ph \cdot CO \cdot OEt + H \cdot SH$$

$$Ph \cdot CO\!|\cdot OH + H\!|SEt \longrightarrow Ph \cdot CO \cdot SEt + H \cdot OH$$
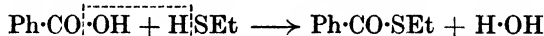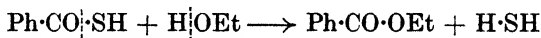
(the second reaction is reversible, but the first is not; in fact the action of hydrogen sulphide upon ethyl benzoate gave benzoic acid and mercaptan). It has now been demonstrated by four methods that, in the esterification of a carboxylic acid, hydroxyl from the acid unites with hydrogen from the alcohol to form water (oxygen from the alcohol passing into the ester), whereas in ester hydrolysis

[55] R. J. Williams, H. K. Mitchell, H. H. Weinstock, and E. E. Snell, *J. Amer. Chem. Soc.*, 1940, **62**, 1784.

[56] H. K. Mitchell, E. E. Snell, and R. J. Williams, *ibid.*, p. 1791.

[1] *J.*, 1912, **101**, 273.

[2] *Amer. Chem. J.*, 1910, **43**, 489.

* Prior to the announcement of the American synthesis [54] T. Reichstein and A. Grüssner (*Helv. Chim. Acta*, 1940, **23**, 650; paper received May 10th, 1940) reported the preparation of methyl *dl*-pantothenate from the racemic lactone, and also methyl *d*-pantothenate from the *l*-lactone; biological assays were not recorded. Following the publication of Stiller's paper,[54] A. Grüssner, M. Gatzi-Fichter, and T. Reichstein (*Helv. Chim. Acta*, 1940, **23**, 1276) repeated the synthesis of methyl *d*-pantothenate and showed that it was biologically active in doses of 10 γ.

the alkoxyl group of the ester is transferred intact to the alcohol. The processes are to be represented

$$R \cdot CO \!-\! OH + H \!-\! OAlk \longrightarrow R \cdot CO \cdot OAlk + H \cdot OH$$

$$R \cdot CO \!-\! OAlk + H \!-\! OH \longrightarrow R \cdot CO \cdot OH + H \cdot OAlk *$$
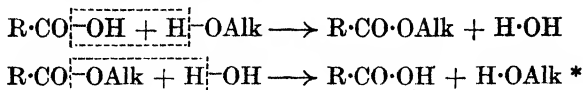
The proof is as follows :

Method I. If the group Alk in the ester $R \cdot CO_2 Alk$ is linked to oxygen by an asymmetric carbon atom, it will not retain its configuration completely if at any stage it becomes free;[3] preservation of asymmetry therefore gives proof that the O–Alk bond is not broken. This was demonstrated for the alkaline hydrolysis of *l*-acetylmalic acid by B. Holmberg,[4] and E. D. Hughes, C. K. Ingold, and S. Masterman[5] have now found a full retention of the configuration of the β-*n*-octyl radical in the esterification of β-*n*-octyl alcohol by acetic acid.

Method II. If the positive alkyl ion is mesomeric, a mechanism of hydrolysis in which this ion becomes free at any stage would lead to a mixture of alcohols. It has been shown that crotyl acetate and α-methylallyl acetate on hydrolysis by alkali[6] or acid[7] yield crotyl and α-methylallyl alcohol respectively, and it may be concluded that the mesomeric ion $MeČH\!-\!CH\!-\!\overset{+}{CH_2}$ never becomes free. Since acid hydrolysis is a reversible process, and much esterification must therefore occur if such a reaction is followed almost to equilibrium, the same conclusion is rendered inevitable for esterification also, for otherwise an indefinite result would have been obtained for acid hydrolysis.[8]

[3] E. S. Wallis and F. H. Adams, *J. Amer. Chem. Soc.*, 1933, **55**, 3838. See R. L. Shriner, R. Adams, and C. S. Marvel in Gilman's " Organic Chemistry," New York, 1938, vol. 1, pp. 303 ff.

[4] *Ber.*, 1912, **45**, 2997.

[5] *J.*, 1939, 840. A small amount of racemisation observed when the esterification was carried out in presence of sulphuric acid indicated the intervention of a subsidiary mechanism in which an alkyl cation dissociates from the alcohol; this is analogous to the S_N1 mechanism of substitution (see below, p. 236).

[6] C. Prévost, *Ann. Chim.*, 1928, **10**, 147.

[7] E. H. Ingold and C. K. Ingold, *J.*, 1932, 756.

[8] S. C. Datta, J. N. E. Day, and C. K. Ingold, *J.*, 1939, 838.

* In nearly neutral solution, the hydrolyses of β-butyrolactone and malolactonic acid appear to occur by a mechanism in which a water molecule withdraws a positive alkyl ion from the ester, $R \cdot CO \cdot O \!-\! Alk + HO \!-\! H \longrightarrow R \cdot CO \cdot OH + HOAlk$ (A. R. Olson and R. J. Miller, *J. Amer. Chem. Soc.*, 1938, **60**, 2687 ; W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J.*, 1937, 1264). This mechanism, however, normally contributes little if anything to ester hydrolysis.

Method III. O. R. Quayle and H. M. Norton [9] have recently esterified *neo*pentyl alcohol with acetic, chloroacetic, dichloroacetic and trichloroacetic acids and hydrolysed the resulting esters with 25% potassium hydroxide solution. In each case the ester showed no unsaturation and the product of hydrolysis was identified as *neo*pentyl alcohol. The work of F. C. Whitmore and his collaborators [10] has shown that a positive *neo*pentyl group invariably rearranges to *tert.*-amyl, the rearrangement being accompanied by the formation of unsaturated derivatives. The conclusion is therefore drawn that the linkage between the *neo*pentyl group and oxygen is maintained throughout both the esterification and the hydrolysis, even when the acid concerned is as strong as trichloroacetic acid.

Method IV. The most direct test employs isotopically distinguished oxygen. M. Polanyi and A. L. Szabo [11] hydrolysed amyl acetate in alkaline solution, using an aqueous medium containing excess of the heavy isotope of oxygen ^{18}O, and found the normal isotope ratio in the amyl alcohol produced; the oxygen of this alcohol must therefore have come from the ^-OAlk group of the ester. More recently, S. C. Datta, J. N. E. Day, and C. K. Ingold [8] have provided a similar demonstration for the acid hydrolysis of methyl hydrogen succinate; the isotopically distinguished oxygen from the solvent again did not appear in the alcohol. The application of the method to an esterification has been made by I. Roberts and H. C. Urey.[12] They esterified benzoic acid with methyl alcohol containing an increased quantity of ^{18}O (in presence of hydrochloric acid), and found that the heavy isotope was not present in the water formed; the oxygen of the water was therefore provided entirely by the benzoic acid.

The three processes esterification (*a*), acid hydrolysis (*b*), and alkaline hydrolysis (*c*),

$$R \cdot C \overset{O}{\underset{OH}{\diagdown}} + H^{\cdot} + HOAlk \underset{(b)}{\overset{(a)}{\rightleftharpoons}} R \cdot C \overset{O}{\underset{OAlk}{\diagdown}} + H^{\cdot} + HOH$$

$$R \cdot C \overset{O}{\underset{OAlk}{\diagdown}} + OH' \overset{(c)}{\longrightarrow} R \cdot CO \cdot O' + HOAlk$$
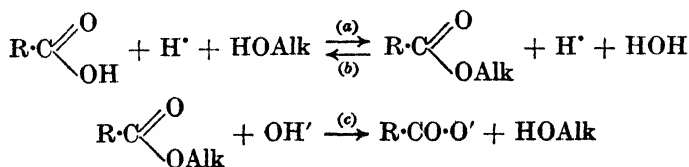
are thus similar in that the linkage between " carbonyl " carbon and " ethereal " oxygen (C–OH or C–OAlk) is severed in each case.

It seems inevitable that in alkaline hydrolysis this fission is

[9] *J. Amer. Chem. Soc.*, 1940, **62**, 1170.
[10] See *ibid.*, 1932, **54**, 3431; 1939, **61**, 1586.
[11] *Trans. Faraday Soc.*, 1934, **30**, 508.
[12] *J. Amer. Chem. Soc.*, 1938, **60**, 2391.

preceded by the co-ordination of hydroxyl ion at " carbonyl " carbon; a molecule of water may also be necessary for the completion of the process, as postulated in T. M. Lowry's mechanism.[13] Since electron-attractive groups in R lower the energy of activation, the main influence of substituents is upon the energy needed to overcome the repulsion between the ion and the ester molecule. This conclusion has been more fully demonstrated by H. O. Jenkins,[14] who finds that the plot of the values of E for the alkaline hydrolysis of a series of p-substituted benzoic esters against the electrostatic potential at the nuclear carbon atom to which the ester group is attached is a straight line of slope approximately Ne (1 faraday); the changes in E are thus to be attributed almost entirely to variations of the work done in bringing up the hydroxyl ion to the ester molecule. The effects of substituents upon alkaline hydrolysis have also been discussed by F. H. Westheimer and M. W. Shookhoff [15] in the light of their experimental results for the rates of hydrolysis of three pairs of compounds, $viz.$, oxamide and sodium oxamate, $tert.$-butyl acetate and $tert.$-butyl chloroacetate, the $tert.$-butyl ester of dimethylglycine and the chloride of the $tert.$-butyl ester of betaine. These pairs illustrate respectively the effects of a negative charge, a dipole and a positive charge. Using the equations developed by J. G. Kirkwood and F. H. Westheimer,[16] which had already been employed with success in connection with the dissociation constants of aliphatic and aromatic acids,[17] they show that the ratio of the rates for each pair is in quantitative accord with the view that the effect of a polar substituent is primarily electrostatic in origin. F. H. Westheimer has used the same equation to calculate the effects of p-substituents upon the alkaline hydrolyses of benzoic, cinnamic, phenylacetic, and β-phenylpropionic esters and of benzamides.[18]

According to the Lowry mechanisms of esterification and acid hydrolysis,[13] the hydrogen ion which here functions as catalyst adds at " carbonyl " oxygen in the former case and at " ethereal " oxygen in the latter. The reason for the difference is not obvious, since the mesomerism of both the carboxyl and the ester grouping renders " carbonyl " oxygen fractionally negative and " ethereal " oxygen fractionally positive in each, and a positive ion is therefore more likely to add at the former. The lack of association in imino-

[13] $J.$, 1925, **127**, 1380. Deuxième Conseil de Chimie Solvay, 1925. Compare W. B. S. Newling and C. N. Hinshelwood, $J.$, 1936, 1357.

[14] $J.$, 1939, 1780.

[15] $J. Amer. Chem. Soc.$, 1940, **62**, 269.

[16] $J. Chem. Physics$, 1938, **6**, 506, 513.

[17] $J. Amer. Chem. Soc.$, 1939, **61**, 555, 1977.

[18] $Ibid.$, 1940, **62**, 1892.

ethers, whereas the isomeric acid amides are associated, also indicates that " ethereal " oxygen is less prone to add a proton than is " carbonyl " oxygen.[19] Accordingly, mechanisms of acid hydrolysis recently put forward postulate addition of the hydrogen ion at the " carbonyl " oxygen in a scheme such as the following : [20, 21]

$$\underset{\substack{\text{HOH}}}{\overset{\substack{O \quad H^+}}{R-\overset{\shortparallel}{C}-OAlk}} \rightleftarrows \underset{\substack{+\\H\overset{}{O}H}}{\overset{\substack{OH}}{R-\overset{|}{\underset{|}{C}}-OAlk}} \rightleftarrows \underset{\substack{HO \quad H}}{\overset{\substack{OH}}{R-\overset{|}{\underset{|}{\overset{+}{C}}}-\overset{+}{O}Alk}} \rightleftarrows \underset{\substack{HO}}{\overset{\substack{O}}{R-\overset{\shortparallel}{C}}} + H^+ + HOAlk$$
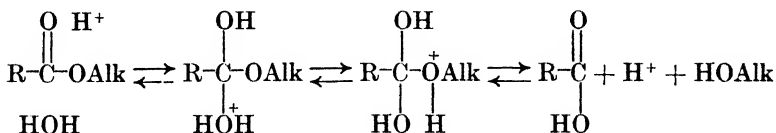
The energy of activation for acid hydrolysis, as for alkaline hydrolysis, is lowered by electron-attractive substituents in R ; [22] the group must therefore influence principally the energy needed for the process of linking a water molecule at " carbonyl " carbon. The values of E are higher for acid hydrolysis than for alkaline hydrolysis, since water is a weaker base than hydroxyl ion, and it is probable that in the former case the energy of activation is used mainly in this process. Now esterification is the exact converse of acid hydrolysis, and its mechanism may be written as in the above scheme, reading from right to left.[23] It is not unreasonable to suppose that the energy of activation is here used mainly in attaching the alcohol molecule to " carbonyl " carbon. Such a view is rendered the more probable by the observation that the kinetics of the two processes have a significant feature in common. The alkaline hydrolysis of nuclear-substituted ethyl benzoates provides one of the familiar examples of reactions in which a substituent well removed from the reactive centre influences the velocity almost entirely by changing the energy of activation; [24] in the acid hydrolysis of the same esters [22] and also in the esterification of the corresponding acids,[25] however, changes in both the energy of activation and the non-exponential term of the Arrhenius equation are found. The changes in E found for the esterification process are both small and irregular.

Kinetic investigations of the esterification of the normal saturated

[19] H. O. Chaplin and L. Hunter, *J.*, 1937, 1114.

[20] O. Mumm, *Ber.*, 1939, **72**, 1874.

[21] G. Davies and D. P. Evans, *J.*, 1940, 339.

[22] E. W. Timm and C. N. Hinshelwood, *J.*, 1938, 862.

[23] The mechanism of esterification has recently been discussed by I. Roberts and H. C. Urey, *J. Amer. Chem. Soc.*, 1939, **61**, 2584.

[24] See *Ann. Reports*, 1938, **35**, 237.

[25] R. J. Hartman and A. M. Borders, *J. Amer. Chem. Soc.*, 1937, **59**, 2107; R. J. Hartman, L. B. Storms, and A. G. Gassmann, *ibid.*, 1939, **61**, 2167; R. J. Hartman and A. G. Gassmann, *ibid.*, 1940, **62**, 1559.

aliphatic acids have been carried out recently by H. A. Smith [26] and by R. A. Fairclough and C. N. Hinshelwood.[27] In methyl-alcoholic solution, and in presence of hydrogen ions or with the aliphatic acid itself as catalyst, there is no important change in the energy of activation as the length of the alkyl chain increases, even up to behenic acid with 22 carbon atoms. The velocity decreases, however, as far as butyric acid, but for the hydrion-catalysed reaction it remains almost constant after this point. The most notable decrease in speed is from propionic to butyric acid, and Smith suggests hydrogen bonding in butyric and higher acids; the " chelate ring " so " completed " is regarded as shielding the carboxyl group from attack, thus reducing the probability factor P of the equation $k = PZe^{-E/RT}$. A similar chelation process in the *anions* of butyric and higher acids was previously postulated by J. F. J. Dippy; [28] according to him, however, its effect is a reduction in the electron-availability of the carboxylate ion, the dissociation constant of the acid thereby being increased above the anticipated value. There is, of course, no evidence that hydrogens of the chain of a saturated aliphatic acid or ester are engaged in such a bonding process, and the suggestion that the hydrogen bonding occurs only in the anion or in the transition complex appears far more probable.[29] Smith finds further that the energy of activation for the esterification of *iso*butyric, *iso*valeric, *iso*-hexoic, phenylacetic, β-phenylpropionic, and γ-phenylbutyric acids has in each case about the same value as for the straight-chain acids (10,000 cals. for esterification with methyl alcohol and hydrogen chloride). Methylethylacetic and β-methylvaleric acids give a slightly higher E, trimethylacetic a perceptibly higher value (11,400 cals.) and diethyl-, dipropyl-, dibutyl-, and di*iso*butyl-acetic acids much larger energies of activation (from 12,400 to 12,900 cals.). When the terminal carbon atoms of diethylacetic acid are linked by a methylene group to give *cyclo*hexanecarboxylic acid, the value of E returns to about 10,000 cals.[30] An interpretation of these results on the basis of the chelation hypothesis is given.

When the carboxylic acid is itself the catalyst (and the esterification therefore bimolecular with respect to it), the decrease in velocity from acetic to butyric acid is followed by a gradual increase as the chain is lengthened. On the basis of experiments with a

[26] *J. Amer. Chem. Soc.*, 1939, **61**, 254, 1176; 1940, **62**, 1136.

[27] *J.*, 1939, 593.

[28] *J.*, 1938, 1222; H. O. Jenkins and J. F. J. Dippy, *J. Amer. Chem. Soc.*, 1940, **62**, 483. See *Ann. Reports*, 1938, **35**, 251.

[29] See D. P. Evans and J. J. Gordon, *J.*, 1938, 1436, 1443.

[30] H. A. Smith and H. S. Levenson, *J. Amer. Chem. Soc.*, 1940, **62**, 2733.

mechanical model resembling that employed by E. Rabinowitch and W. C. Wood [31] to illustrate collision frequencies in a closely-packed medium, Fairclough and Hinshelwood conclude that, when the molecule of the solute becomes very large, there is an increase in the number of repeated collisions, and the observed rise in velocity with length of chain is therefore to be ascribed to an increase in the value of Z.

For the alkaline hydrolysis of the normal aliphatic esters, the steady increase in the energy of activation to a constant maximum value quite early in the series (at about ethyl n-valerate), which had previously been indicated by experiments in 85% alcohol,[32] has been confirmed by measurements in 70% aqueous acetone,[21] where the differences are much larger than in the earlier work. A more marked increase in E occurs in the series acetate$<$isobutyrate$<$ trimethylacetate $<$ diethylacetate,[21] and dipropyl- and dibutyl-acetic esters give high values similar to that found for the diethyl-acetate; [33] the high value is not found for the $cyclo$hexanecarboxyl-ate.[30] The energies of activation for the acid hydrolysis of the normal esters are equal within the limits of experimental error, but the isobutyrate now gives a lower value and the trimethyl-acetate and diethylacetate high values (as for esterification and alkaline hydrolysis).

R. A. Fairclough and C. N. Hinshelwood's study of the alkaline hydrolysis of ethyl benzoate in various alcohol–acetone–water mixtures showed that both the energy of activation and the PZ term of the kinetic equation are influenced by changes of solvent,[34] and this has been confirmed by R. A. Harman by measurements of the speed of alkaline hydrolysis of ethyl benzoate and of ethyl m-nitrobenzoate in aqueous alcohol and aqueous acetone of various compositions.[35] D. P. Evans and H. O. Jenkins now find that an approximately linear relationship exists, for each of Harman's series of measurements, between the values of the activation energy and the reciprocals of the dielectric constant of the medium.[36] Following C. N. Hinshelwood, K. J. Laidler, and E. W. Timm's division of the activation energy into bond-stretching and repulsion

[31] *Trans. Faraday Soc.*, 1936, **32,** 1381; 1937, **33,** 1225.

[32] D. P. Evans *et al.*, *J.*, 1938, 1439. The small differences observed in 85% alcohol had led H. A. Smith and co-workers (*J. Amer. Chem. Soc.*, 1939, **61,** 1172, 1963) to regard the values of E as constant throughout.

[33] H. S. Levenson and H. A. Smith, *J. Amer. Chem. Soc.*, 1940, **62,** 1556. These workers also find equal energies of activation for butyrate, laurate, and isohexoate in 85% alcohol, and a rather higher value for β-methylvalerate and $cyclo$hexylacetate (*ibid.*, p. 2324).

[34] *J.*, 1937, **538.**   [35] *Trans. Faraday Soc.*, 1939, **35,** 1336.

[36] *Ibid.*, 1940, **36,** 818.

energy,[37] they write the equation $E = E_B + E_R = E_B + E_X/\varepsilon$, the bond-stretching energy E_B being regarded as independent of solvent for a series of solvents of the same type (*e.g.*, different alcohol-water mixtures), whereas the repulsion energy is inversely proportional to the dielectric constant. By extrapolation of their graph to $1/\varepsilon = 0$, they deduce values for the two portions of the activation energy, and find that these values are influenced in the anticipated (opposite) directions by the *m*-nitro-substituent. Thus, E_B is raised somewhat, whereas E_R is decreased very powerfully by this electron-attractive group. It is further suggested that constancy of E for different solvents (and sometimes also for the gas phase) is to be expected when practically the whole of the energy of activation is to be described as "bond-stretching energy." Evans and Jenkins point out that, in view of the dependence of the dielectric constant upon temperature, the evaluation of energies of activation from the slope of the plot of log k against $1/T$ leads, theoretically, to inaccurate values, although the errors are probably relatively small as a rule, and the values are comparable if not absolute.

Aliphatic Substitution.—In a substitution reaction one group is removed and another added, and mechanisms may be envisaged in which these processes occur either simultaneously or consecutively. The work of C. K. Ingold, E. D. Hughes and their collaborators, described in the *Annual Reports* for 1938,[38] has shown that nucleophilic substitutions can and actually do proceed in accordance with either of these mechanisms, the predominance of one or the other being determined by the nature of the compound in which substitution occurs, the nucleophilic activity and the concentration of the substituting agent, and the character of the solvent. The hydrolysis of an alkyl halide RX provides a specific instance, and is formulated as follows :

$$\left. \begin{array}{l} RX + OH' \longrightarrow R{\cdot}OH + X' \\ RX + H{\cdot}OH \longrightarrow R{\cdot}OH + X' + H^{\boldsymbol{\cdot}} \end{array} \right\} \quad \cdot \quad \cdot \quad S_N2$$

or

$$\left. \begin{array}{l} RX \xrightarrow{\text{slow}} R^{\boldsymbol{\cdot}} + X' \\ R^{\boldsymbol{\cdot}} + OH' \xrightarrow{\text{rapid}} R{\cdot}OH \\ R^{\boldsymbol{\cdot}} + H{\cdot}OH \xrightarrow{\text{rapid}} R{\cdot}OH + H^{\boldsymbol{\cdot}} \end{array} \right\} \quad \cdot \quad \cdot \quad S_N1$$

followed by

or
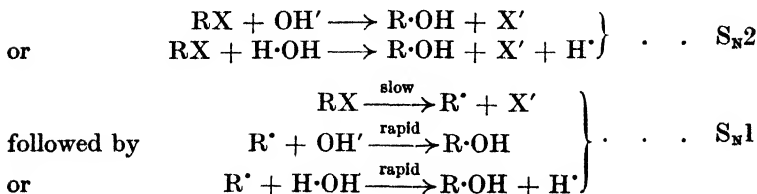
If both reagents are present at small and controllable concentration, the changes here represented will be kinetically of the second (S_N2) and first (S_N1) order respectively. If, however, the hydrolysis occurs in an aqueous medium, one reagent is the solvent, which is present in large excess, and the application of elementary

[37] *J.*, 1938, 848.   [38] *Ann. Reports*, 1938, **35**, 210 *ff.*

principles shows that *both* mechanisms now require first-order kinetics; the obvious conclusion is that the kinetic order of such a solvolytic reaction provides no criterion of mechanism. Evidence relating to the mechanism of solvolytic processes was nevertheless obtained by Ingold, Hughes, and co-workers [38] by studies of the effects upon the reaction rate of changes in the structure of the alkyl halide, the substituting agent, and the solvent, of the effects of solvent changes upon the product, and of the stereochemical course of the substitution. The conclusion was reached that, in aqueous alcohol or aqueous acetone, the solvolytic reactions of methyl and ethyl halides occur by the bimolecular mechanism S_N2 and those of *tert.*-butyl (and other tertiary) halides by the unimolecular mechanism S_N1, while both mechanisms are of comparable importance in the solvolysis of *iso*propyl (and other purely aliphatic secondary) halides; benzhydryl and α-phenylethyl halides react by the unimolecular mechanism.[38]

Reference was made in the *Annual Reports* for 1938 to the objection that energies of ionisation must be of the order of 200,000 cals., which is far higher than any thermal activation energy accessible at the ordinary temperature. The figure applies, however, to gaseous ionisation, and Hughes and Ingold pointed out in 1935 that the unimolecular mechanism must be regarded as made possible by solvation; the correctness of such a view is indicated by the fact that solvation can break down the lattices of ionised crystals which have lattice energies of about the same order of magnitude. R. A. Ogg [39] has calculated that, even when the solvation energy is allowed for, the activation energy demanded (50,000 to 70,000 cals.) is still too high to admit of measurable rates at the ordinary temperature. His argument, however, introduces various assumptions of an uncertain character, and in any case it applies to the reactions of the methyl halides in aqueous solutions, where no evidence of a unimolecular mechanism has ever been found or claimed.[40]

A study of the products formed in the combined hydrolysis and alcoholysis of *tert.*-butyl chloride [41] showed that the method of approach by which A. R. Olson and R. S. Halford had claimed to have established a bimolecular mechanism for all solvolytic reactions of alkyl halides [42] actually makes a bimolecular (*i.e.*, single-stage) mechanism inadmissible, but does not conflict with the

[39] *J. Amer. Chem. Soc.*, 1939, **61**, 1946.
[40] Compare P. D. Bartlett and L. H. Knox, *ibid.*, p. 3188.
[41] L. C. Bateman, E. D. Hughes, and C. K. Ingold, *J.*, 1938, 881. See *Ann. Reports*, 1938, **35**, 218.
[42] *J. Amer. Chem. Soc.*, 1937, **59**, 2644.

requirements of the unimolecular mechanism according to which there need be no direct connection between reaction rate and product composition. This conclusion is now confirmed by P. D. Bartlett,[43] who has shown that the dependence of product composition upon the proportions of alcohol and water in the solvent is consistent with the view that the rate-determining stage is an ionisation. S. Winstein [44] has suggested that Olson and Halford's rate formula should be applied on the basis of a termolecular or quadrimolecular mechanism with two or three molecules of solvent as reactant, but it is now pointed out [45] that the agreement obtained between theory and experiment is of little significance in view of the paucity of available data and the latitude which the method consequently allows in the selection of arbitary constants.

The unimolecular character of the *non-solvolytic* hydrolysis of *tert.*-butyl chloride was established, by L. C. Bateman and E. D. Hughes, for the case where the alkyl halide was caused to react with small quantities of water in formic acid as solvent; *tert.*-butyl alcohol was isolated as product under these conditions, together with some *iso*butylene, but a mere trace of *tert.*-butyl formate.[46] These results have been completely confirmed,[47] and it has been shown that the trace of alkyl formate may be ascribed to the subsequent esterification of a small proportion of the *tert.*-butyl alcohol. Further, the introduction of formate or chloroacetate ions leads to the production in quantity of *tert.*-butyl formate or chloroacetate as the case may be, but the rate of appearance of halide ions is not increased; the measured velocity is still, therefore, that of the ionisation of the *tert.*-butyl chloride, and hence the reaction of alkyl halide with the anion, like its hydrolysis, is unimolecular. In contrast with this, when *n*-butyl bromide reacts with small quantities of water in formic acid solution, the speed increases linearly with the water concentration, and added formate ions give a marked acceleration.[48] The reactions of the primary halide, both with water and with the anion, are thus largely bimolecular, although there are definite indications of a simultaneous unimolecular hydrolysis which is slower by a factor of about 10^6 than the unimolecular hydrolysis of *tert.*-butyl chloride (in accordance with the theory of Hughes and Ingold).

[43] *J. Amer. Chem. Soc.*, 1939, **61**, 1630.   [44] *Ibid.*, p. 1635.

[45] L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *J.*, 1940, 1009.

[46] *J.*, 1937, 1187. See *Ann. Reports*, 1938, **35**, 216.

[47] L. C. Bateman and E. D. Hughes, *J.*, 1940, 935.

[48] *Idem, ibid.*, p. 940.

When an alkyl halide reacts with small quantities of water in formic acid medium, the conditions are peculiarly favourable to the unimolecular mechanism, for the substituting agent is one of weak nucleophilic activity, at low concentration and in a solvent of good ionising power. Using formic acid containing about 0·5% and also 10% of water, Bateman and Hughes have been able to realise the theoretical order of velocities for the unimolecular mechanism throughout the series Me $<$ Et $<$ Pr$^\beta$ $<$ tert.-Bu.[49] A fuller investigation of the reaction of methyl bromide indicated that bimolecular substitution occurs simultaneously, but the contribution of this mechanism is not sufficiently great to introduce a rate minimum into the series, as it does when aqueous alcohol or aqueous acetone is used.

Recent papers by Hughes, Ingold, and co-workers [50] have shown that the evidence submitted by W. Taylor [51] in favour of a bimolecular mechanism for all these nucleophilic substitutions is based upon an incorrect interpretation of kinetic data, and that the calculations of equilibrium concentrations for acetone solutions containing tert.-butyl or benzhydryl chloride and small quantities of water are valueless on both experimental and theoretical grounds. It is further pointed out that, when small quantities of a solvent which strongly favours a reaction, but does not appear in the equation as a reagent, are added to one in which the change is very slow, proportionality between reaction rate and concentration of the " active " solvent is to be expected (the reaction becomes " pseudobimolecular "), provided the " active " solvent be present in sufficiently small amount. An example of such behaviour was observed by N. T. Farinacci and L. P. Hammett,[52] who studied the reaction of benzhydryl chloride with ethyl alcohol containing various small percentages of water. As the proportion of added water was increased, the velocity at first rose linearly with the concentration of water, but this was not due to the superposition of a bimolecular hydrolysis on the alcoholysis, for examination of the product showed that practically the whole effect of the added water was an acceleration of the alcoholysis. Although, therefore, the reaction induced by the added small amount of water is experimentally of the second order (the velocity being proportional to the concentrations of benzhydryl chloride and water), it cannot be

[49] J., 1940, 945.

[50] L. C. Bateman, K. A. Cooper, and E. D. Hughes, ibid., p. 913; M. G. Church, and E. D. Hughes, ibid., p. 920; L. C. Bateman, K. A. Cooper, E. D. Hughes, and C. K. Ingold, ibid., p. 925.

[51] See Ann. Reports, 1938, **35**, 215; J., 1939, 478, 1872.

[52] J. Amer. Chem. Soc., 1937, **59**, 2542.

described as a bimolecular reaction, since water is proved not to enter into the chemical equation.

A recent and exceedingly interesting development of the work of Ingold, Hughes, and co-workers has led to a kinetic demonstration of the unimolecular character of the hydrolyses of *tert.*-butyl, benzhydryl, *p*-alkylbenzhydryl, and *pp'*-dialkylbenzhydryl halides in aqueous acetone.[53] Although on elementary grounds such solvolytic reactions require first-order kinetics whether they proceed by the unimolecular or by the bimolecular mechanism, new evidence has been obtained by the observation of certain deviations from strictly first-order kinetics which are to be anticipated when the mechanism is unimolecular but not when it is bimolecular.* The influences of added salts upon the reaction rate and upon the products have also provided evidence of the unimolecular mechanism.

The hydrolysis of a halide RX by the unimolecular mechanism is represented as follows : †

$$ RX \underset{(2)}{\overset{(1)}{\rightleftarrows}} R^{\textbf{·}} + X' \overset{HOH}{\underset{(3)}{\longrightarrow}} ROH + H^{\textbf{·}} + X' $$
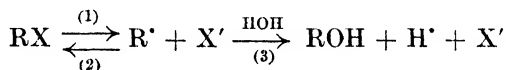
Since the first (slow) stage is reversible, and the accumulation of halide ions as reaction proceeds will increase the importance of reaction (2), the velocity coefficient, determined by following the changes in concentration of hydrogen or halide ions, will be progressively reduced without any reversal of the complete change. This " mass law effect " will be absent only if reaction (3) is very rapid as compared with reaction (2). There will be no such retardation in a reaction by the bimolecular mechanism, which will proceed at a steady first-order rate.

The influence of an added electrolyte (metallic salt) will depend

⸮ [53] L. C. Bateman, E. D. Hughes, and C. K. Ingold, *J.*, 1940, 960, 974 ; M. G. Church, E. D. Hughes, and C. K. Ingold, *ibid.*, p. 966 ; M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *ibid.*, p. 971 ; L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *ibid.*, p. 979.

* The failure of such deviations to excite comment in the course of earlier work by Hughes and Ingold was due to the fact that they were rendered very small by the nature of the halides (*tert.*-butyl) to which chief attention was directed, by the small concentrations used, and by the particular solvent mixtures in which the experiments were made. Nevertheless, deviations from accurate first-order kinetics in some measurements on α-phenylethyl chloride were reported by E. D. Hughes, C. K. Ingold, and A. D. Scott (*J.*, 1937, 1201).

† Reaction (3) is here written as irreversible. If a hydrolysis is appreciably reversible under the experimental conditions, the forward reaction can be isolated by application of the appropriate kinetic expression.

upon the identity or otherwise of the anion introduced with that produced by the alkyl halide. If the two are the same (*e.g.*, if RBr is hydrolysed in presence of NaBr), the speed of a reaction by the unimolecular mechanism will be decreased owing to more extensive reassociation of the ions (reaction 2), but a change by the bimolecular mechanism will be subject to no such effect. The addition of a salt having an anion (Y′) different from that (X′) given by the alkyl halide RX will leave the initial rate of destruction of RX unchanged if the reaction occurs by the unimolecular mechanism, for, even though RY may be formed in addition to ROH, this rate will still be that of the ionisation of RX. The effect observed at later stages of the reaction, however, will depend upon the character of the alkyl derivative RY. If this is hydrolysed to ROH more rapidly than RX is, the retardation due to the reversal of ionisation by the anion formed (X′) will be diminished in proportion as Y′ competes with X′ for the organic cation R˙. If RY is hydrolysed less rapidly than RX, the velocity of hydrolysis (measured by the increase of acidity) will be subject to an additional retardation. Finally, if RY is not hydrolysed under the experimental conditions, the rate of hydrolysis (again measured by the increasing acidity) will be reduced to zero before an equivalent of acid has developed, while the speed of destruction of RX, measured by the appearance of X′ ions, will, on the contrary, show a diminished retardation inasmuch as the opportunity of the anion X′ to reverse the ionisation will be made smaller by the competing attack of Y′; moreover, the proportions in which ROH and RY are formed will have a special significance (see below). In contrast with these varied effects of salts upon a reaction by the unimolecular mechanism, a bimolecular change would in every case be accelerated throughout by a non-common-ion salt, since the attack of the foreign anion upon the alkyl halide would be added to the hydrolysis; again the proportions of the two products are of importance.

There is, however, a second source of deviation from strictly first-order kinetics. This arises from the increasing ionic strength of the solution as the solvolytic substitution of the neutral alkyl halide proceeds, and it leads to a progressive rise in the first-order coefficient. The addition of any electrolyte also leads to an increase in speed for the same reason. The unimolecular (ionic) mechanism is likely to be far more sensitive to this " ionic strength effect " than is the bimolecular.*

The anticipated variations of the first-order velocity coefficients

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* This has since been confirmed (private communication from Professor Ingold).

for the unimolecular and bimolecular mechanisms are summarised
in the table below.

Mechanism.	Salt added.	Ionic strength effect.	Mass law effect.
S_N1	None	Progressive rise	Progressive fall
	Common ion	Increase	Decrease
	Non-common ion	Increase	None initially; progressive fall modified
S_N2	None	Small progressive rise	None
	Common ion	Small increase	None
	Non-common ion	Small increase	Increase

The combination of mass-law and ionic strength effects has been
observed by Ingold, Hughes, and co-workers in the reactions of
the alkyl halides referred to above, and the results have further
been shown to be quantitatively in agreement with theoretical
considerations (see later).   G. W. Beste and L. P. Hammett,[54] too,
have recorded certain effects of added salts upon the hydrolysis of
benzyl chloride in aqueous dioxan (e.g., sodium chloride and sodium
acetate lead to a decreased, and sodium perchlorate to an increased
speed), which are doubtless to be interpreted along similar lines
(the authors themselves suggest that chloride or acetate ions cause
ionic reassociation).   A mass-law effect also appears to be shown
in the results of P. D. Bartlett and R. W. Nebel [55] upon the methyl
alcoholysis of p-methoxybenzhydryl chloride in nitrobenzene solu-
tion; this effect was no doubt magnified by the presence in their
solutions of triethylamine, which was introduced in order to
eliminate the reversed change, but which would also replace
covalent hydrogen chloride by the ionised amine hydrochloride.

The following is an outline of the recent work of Ingold, Hughes,
and co-workers,[53] in which the anticipated effects set out in the
above table are fully illustrated.   The hydrolysis of tert.-butyl
bromide (0·1M; this is a higher concentration than was used in the
earlier work, the effects thereby being magnified) in 90% and in
70% aqueous acetone gives first-order velocity coefficients (deter-
mined by measurements of the developing acidity) which rise
steadily as reaction·proceeds.   The increase in the values of the
coefficients is in agreement with that calculated theoretically on
the postulate that a pure ionic strength effect is being observed,
the mass law effect being inconsiderable.   Added salts (lithium
bromide, lithium chloride, and sodium azide at 0·1M-concentration
in 90% aqueous acetone at 50°) increase the initial rate of dis-
appearance of the halide (measured for lithium bromide and
chloride by the increase of acidity and for sodium azide by the
increase of halide concentration; see below) by a factor of about

1·4, and this is also in good agreement with calculations based upon a pure ionic strength effect. The reader is referred to the original papers for the actual calculations. Lithium bromide also reduces the upward drift of the velocity coefficients, owing to the smaller proportionate change of ionic strength, but in presence of lithium chloride there is a downward drift towards the end of the change, since some *tert.*-butyl bromide is replaced by *tert.*-butyl chloride, which hydrolyses more slowly. The real, though not powerful, intervention of anions is demonstrated by the observations made in presence of sodium azide. There are here two final products, since *tert.*-butyl azide is not hydrolysed under the experimental conditions. The total speed of removal of alkyl bromide is now determined as the rate of appearance of bromide ions, the velocity coefficients for which remain fairly constant throughout the reaction. The speed of actual hydrolysis is determined as the rise in acidity; this is initially about 5% less than the total rate of disappearance of *tert.*-butyl bromide, and it falls towards the end, reaching zero when 94% of the theoretical quantity of *tert.*-butyl alcohol has been formed.

The mass law effect is observed, in addition to the ionic strength effect, in the hydrolyses of benzhydryl halides; in the case of the bromide the former compensates the latter, giving steady velocity coefficients. In 90% aqueous acetone at 50°, non-common-ion salts (0·1M) increase the initial velocity by a factor of about 2 (ionic strength effect), but a common-ion salt reduces it somewhat owing to the superimposed mass law effect which here predominates. Still larger effects are observed in *p-tert.*-butylbenzhydryl and *p*-methylbenzhydryl chlorides and especially in *pp'*-dimethylbenzhydryl chloride. In the last case the first-order coefficients fall rapidly (mass law effect) even at concentrations of 0·04—0·05M, where in the other instances the first-order law is followed with fair accuracy. The acceleration by non-common-ion salts and the retardation by common-ion salts are also more powerful. Throughout the instances examined, the effects of added electrolytes in increasing the reaction rate by their contributions to the ionic strength of the solutions, and the variations with concentration, solvent and temperature, are in agreement with the theory outlined above. The superimposed effect of salts having an anion in common with that given by the alkyl halide, which is to depress the rate, is also in agreement with theory.

An expression for the ionic strength effect having been derived, and this having been found to be in agreement with the experimental figures for *tert.*-butyl bromide (see above), the next step in the quantitative treatment of the problem is the calculation of the

anticipated decrease in speed for different values of the ratio k_2/k_3,[*] which is the essential measure of the mass law effect. The combination of ionic strength and mass law effects should then lead to a variation of the velocity coefficients lying between the ascending series calculated for the former and the descending series calculated for the latter. The actual calculation of the combined influence is not a simple matter, however, for the superimposed effects are not independent; the ionic strength effect can influence k_2 and k_3 differently, thus modifying the measured rate. In order to deal quantitatively with these rather complicated influences, it is necessary to make some postulate regarding the manner in which the R⁺ cation is hydroxylated (reaction 3). Four possibilities are considered : (a) reaction (3) may be unimolecular with respect to water; (b) it may be multimolecular with respect to water; (c) the alkyl cation may be attacked by a hydroxide ion, and (d) the cation may be attacked by a hydroxide ion in collaboration with water molecules. Hypothesis (b) appears the most probable for several reasons. First, the cation is highly energised and the time lag between reactions (1) and (3), which mechanism S_N1 implies, is probably due to the small statistical probability of the transition state of (3), which indicates a more complex configuration than is possible for $(R \ldots OH_2)^+$. Secondly, many water molecules must contribute the activation energy necessary for the ionisation in reaction (1), and the cation is therefore formed within an aqueous solvation shell; [†] since all the elements necessary for reactivity are present within this shell, it is probable that its career will end by a collapse rather than by the entry of an energised water molecule or hydroxyl ion from outside. Thirdly, experiment shows that the proportions of dimethylbenzhydryl chloride which react with water and azide ions in aqueous acetone are independent of the concentration of water over the five-fold range investigated. The proof of hypothesis (b) is obtained by the derivation of equations for the velocity coefficients in accordance with each of the hypotheses :

[*] k_2 and k_3 are the velocity coefficients of reactions (2) and (3) respectively of the scheme on p. 240.

[†] For this reason, N. T. Farinacci and L. P. Hammett (ref. 52) describe the mechanism as "polymolecular". P. D. Bartlett and R. W. Nebel, in their study of the reaction of p-methoxybenzhydryl chloride with methyl alcohol (ref. 55), find their results to be in harmony with an equation derived on the supposition that, under their conditions, either one or two molecules of alcohol are involved. In agreement with Farinacci and Hammett, they believe that the halogen is removed as a solvated anion, and they suggest that at higher concentrations of alcohol more highly solvated anions will be formed, the reaction becoming polymolecular (in the sense intended by Farinacci and Hammett).

the experimental figures fit hypothesis (b) and this alone. Agreement is found for dimethylbenzhydryl chloride (where both effects are unusually powerful) in three different media, and also for the remaining halides where both the mass law and the ionic strength effect are of importance. In all these instances, therefore, the deviations from the first-order law are just those which are predicted on the basis of the unimolecular mechanism. When similar principles are applied to the calculation of velocities in the presence of added salts, substantial agreement between theoretical and experimental values is again found, at least for the earlier stages of the reactions.

A further test has been carried out by the correlation of reaction rates with the composition of the product in presence of added anions which give a stable alkyl derivative. Sodium azide was the salt used, and there are now two final products, ROH and RN_3. In a reaction by the unimolecular mechanism these are formed in a stage other than that which controls the velocity, and there need therefore be no connection between their proportions and the measured reaction rate; the bimolecular mechanism, on the other hand, demands a definite and simple relationship between velocity and product composition, since the measured speed is that of the reaction which itself leads directly to the products. The results for *tert.*-butyl bromide, *p-tert.*-butylbenzhydryl chloride and dimethylbenzhydryl chloride (the last-named was investigated in three media) show that no connection exists between the proportion of alkyl azide formed and that calculated from the velocity on the basis of a bimolecular change. The principle is the same as that applied by Bateman, Hughes, and Ingold to the products obtained when different mixtures of reactive solvents were used.[41] On the other hand, if parallel reactions are carried out (again in presence of a salt giving a stable derivative) for two halides having the same alkyl group (*e.g.,* RCl and RBr), the unimolecular mechanism requires that the composition of the product should be the same in each case, for they are formed from the same alkyl cation ; this identity of product is not to be expected in the bimolecular mechanism. Products identical within experimental error (containing respectively 34% and 34·5% of alkyl azide) were obtained from benzhydryl chloride and bromide in presence of sodium azide. This test may be compared with that applied in the examination of simultaneous unimolecular substitution and elimination reactions, where the ratio of the velocity of elimination to the total velocity was the same for different halides having the same alkyl group.[56] The observations here referred to indicate the operation

[56] See *Ann. Reports*, 1938, **35**, 227.

of the unimolecular mechanism both in hydrolysis and in substitution by anions, for different results would have been obtained if *either* reaction had been bimolecular.

The results of this detailed investigation of the solvolytic substitutions of alkyl halides can leave no doubt regarding the existence of the unimolecular mechanism in these reactions; the direct proof of an ionisation mechanism is now added to the previous, less direct evidence, and the number of instances to which the test has been applied with positive results is sufficient to demonstrate the importance of this mechanism in the solvolytic reactions of aliphatic compounds. L. C. Bateman, E. D. Hughes, and C. K. Ingold have followed up this work by a demonstration of the applicability of the same method to the direct proof of the unimolecular mechanism of a non-solvolytic substitution, *viz.*, halogen exchange between an alkyl halide and halide ions; the non-solvolytic hydrolysis of *tert.*-butyl chloride in formic acid medium had already been shown to be of the unimolecular type.[57] The new work was preceded by a semi-quantitative study of the velocities of several substitution reactions of benzhydryl and *m*-chlorobenzhydryl chlorides in liquid sulphur dioxide medium.[58] They include the reactions of the halides with fluoride ions, iodide ions, pyridine, and triethylamine, the velocities being determined by observations of the change in conductivity of the solution with time. Were these substitutions all one-stage bimolecular processes, they would occur at rates varying over several powers of ten; their unimolecular character under the conditions of experiment is shown by the substantial equality of their initial rates. The reaction of the halide with water is apparently rather faster than the others, but this may be ascribed to the low degree of ionisation of hydrogen chloride in liquid sulphur dioxide and its consequent variation during the reaction. A detailed and quantitative study has as yet been made in the case of one reaction only—that of *m*-chlorobenzhydryl chloride with tetramethylammonium fluoride.[59] The ionic strength and mass law effects can here be separated easily and each studied without interference from the other, and the results are in excellent agreement with theoretical anticipations based upon the unimolecular mechanism. The ionic strength effect is unusually large, and can be observed, without appreciable interference by the mass law effect, by study of the variation of initial velocity with the concentration of fluoride ions (this method of attack was clearly impossible in the solvolytic reactions referred to above); the variation is found to follow the

[57] See above, p. 238.   [58] *J.*, 1940, 1011.
[59] *Ibid.*, p. 1017.

law required for a pure ionic strength effect. Then, the ionic strength does not change during the course of the reaction

$$RCl + F' \longrightarrow RF + Cl'$$
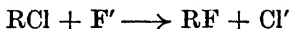
and the form of the reaction curve therefore provides a basis for the study of the mass law effect. This effect is very large, for the rate of reaction (2) in the scheme below is considerably greater than that of reaction (3) :

$$RCl \underset{(2)}{\overset{(1)}{\rightleftarrows}} R^{\cdot} + Cl' \xrightarrow[F']{(3)} RF + Cl'$$
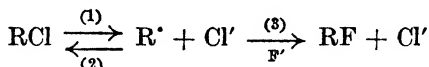
It is calculated, indeed, that chloride ions attack the alkyl cation twenty times faster than fluoride ions do. Initially the whole of the alkyl cation will be converted into alkyl fluoride, but the proportion which gives RF will become progressively smaller as the concentration of chloride ion increases, and a reaction starting quite rapidly ends relatively slowly. The same effect is observed if tetramethylammonium chloride is added initially, a 0·04M-concentration of the salt depressing the speed to 1/150 of its value in absence of the salt. The observed kinetics are accounted for quantitatively on the basis of the unimolecular mechanism (see original paper for details of calculation). A further step has thus been taken towards the demonstration of the importance of the unimolecular mechanism throughout aliphatic substitutions, solvolytic and non-solvolytic, when the conditions are such as to favour the ionisation of the compound in which the substitution occurs.

Four instances of the replacement of a halogen by one of the same kind have been studied by S. Sugden and co-workers,[60] who have conducted kinetic investigations of the exchange reactions of *n*-propyl, *n*-butyl, *iso*propyl, and *iso*butyl bromides with radioactive bromide ions in 90% acetone :

$$RBr + Br^{*'} \rightleftarrows RBr^{*} + Br'$$
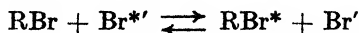
They find that the reactions follow the bimolecular law, as would be expected. The energies of activation stand in the order *n*-Pr $\langle$ *n*-Bu $\langle\langle$ *iso*Bu $\langle\langle\langle$ *iso*Pr.

Tautomeric Effects of Alkyl Groups.—The suggestion made by J. W. Baker and W. S. Nathan [61] to account for observed deviations of alkyl groups from the order of their inductive effects (Me $<$ Et $<$ *iso*Pr $<$ *tert.*-Bu) has been referred to in an earlier report.[62]

[60] L. J. le Roux and S. Sugden, *J.*, 1939, 1279; G. A. Elliott and S. Sugden, *ibid.*, p. 1836.

[61] *J.*, 1935, 1844; J. W. Baker, *J.*, 1939, 1150.

[62] *Ann. Reports*, 1938, **35**, 249.

A partial conjugation of the C–H electron pairs with an attached unsaturated system would lead to an effect superimposed upon the inductive effect, but *decreasing* in magnitude in the order Me $>$ Et $>$ *iso*Pr $>$ *tert.*-Bu, and the sum of the permanent (mesomeric) and time-variable (electromeric) components of such an effect is conveniently termed the tautomeric effect of the group. Evidence for the existence of such an effect has come from studies of both velocities and equilibria, but until very recently no instance was found where the tautomeric displacements were sufficiently important relative to the inductive effects to give the order appropriate to the former. Thus, the values of the dipole moments of the alkylbenzenes (PhMe 0·37, PhEt 0·58, PhPr$^{\beta}$ 0·65, PhBu$^{\gamma}$ 0·70 in the vapour phase [63]) afford one further example of the normal sequence, and in cases where disturbance of this order has been detected the differences have been small and any inversion incomplete. In the course of their work on aliphatic substitution, E. D. Hughes, C. K. Ingold, and N. A. Taher [64] have now measured the velocities of hydrolysis of the *p*-alkylbenzhydryl chlorides in 80% aqueous acetone. The reactions are unimolecular (the measurable stage is $RCl \rightarrow R^{\cdot} + Cl'$) and are so strongly electron-demanding that a very considerable magnification of the tautomeric effect is to be anticipated. This expectation is borne out by the experimental results; the order of the total effects of the groups studied is Me $>$ Et $>$ *iso*Pr $>$ *tert.*-Bu $>$ H, the velocities being spread over a range of 1 to 30. Alcoholysis gives the same sequence, but the values are placed more closely. The actual figures are as follows :

	Me.	Et.	*iso*Pr.	*tert.*-Bu.	H.
Hydrolysis, $10^6 k$ at $0°$	83·5	62·6	46·95	35·9	2·82
Alcoholysis, $10^5 k$ at $25°$	123	120	106	98·7	5·30

It has further been shown that complete loss of a proton does not occur at any stage,[65] for when the hydrolysis of *p*-methylbenzhydryl chloride was carried out in an acetone–deuterium oxide medium the *p*-methylbenzhydrol, after isotopic normalisation of its hydroxylic hydrogen, was completely free from deuterium. The work described above provides the first really satisfactory evidence of the existence of alkyl conjugation as envisaged by Baker and Nathan.

Elimination Reactions.—Reference was made in the *Annual Reports* for 1938 [66] to the two mechanisms, E_1 and E_2, by which

[63] J. W. Baker and L. G. Groves, *J.*, 1939, 1144.

[64] *J.*, 1940, 949.

[65] A possibility suggested by Sir R. Robinson, *Chem. and Ind.*, 1936, **55**, 962.

[66] *Ann. Reports*, 1938, **35**, 226.

olefins may be formed from alkyl halides and other compounds. These are the analogues of the S_N1 and S_N2 mechanisms of substitution; they are represented in the following manner :

$$\left.\begin{array}{c} \text{H—CR}_2\text{—CR}_2\text{—X} \xrightarrow{\text{slow}} \text{H—CR}_2\text{—CR}_2{}^+ + \text{X}^- \\ \text{H—CR}_2\text{—CR}_2{}^+ \xrightarrow{\text{rapid}} \text{H}^+ + \text{CR}_2 = \text{CR}_2 \end{array}\right\} \quad . \quad \text{E}_1$$

$$\text{HO}^- + \text{H—CR}_2\text{—CR}_2\text{—X} \longrightarrow \text{HOH} + \text{CR}_2 = \text{CR}_2 + \text{X}^- \quad . \quad \text{E}_2$$
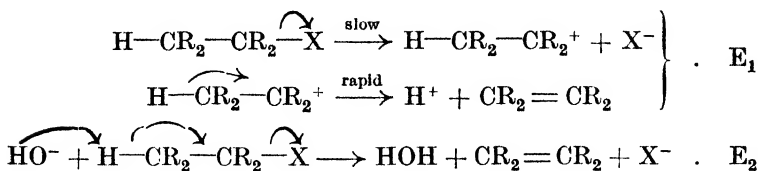
Extending the earlier work in this field, E. D. Hughes, C. K. Ingold, S. Masterman, and B. J. McNulty [67] have shown how apparently inconsistent observations in the older literature can now be understood in the light of the two mechanisms and the effects thereon of chemical structure, the nature of the reagent and of the solvent, concentration, and temperature.

C. R. Hauser [68] has contributed a general discussion of reactions which involve the removal of a proton and an anionic group, with or without rearrangement. Three steps are involved : the release of the anion, the release of the proton, and stabilisation of the residue. When the change is brought about by an acidic reagent, the first step is the removal of the anion as in the pinacol–pinacolone rearrangement; [69] the loss of an anion is also the first step in olefin elimination by the E_1 mechanism (above). If the reagent is a base, the first step is the removal of a proton, and two extreme cases are distinguished. In " type 1," the equilibrium lies strongly on the side of the salt, as in bromoamides and hydroxamic acids, where elimination of hydrogen bromide and water respectively is accompanied by rearrangement; in " type 2," salt formation is négligible, as in the removal of halogen acid from an alkyl halide by the E_2 mechanism. Changes of " type 1 " exhibit unimolecular kinetics, the measured speed being that of the decomposition of the anion (with rearrangement in the instances cited above), whereas changes of " type 2 " are bimolecular, the three processes being simultaneous as in the E_2 mechanism (above). The manner in which the residue is stabilised depends upon the nature of the system, and Hauser considers various cases which he illustrates by examples. If the proton and the anion are removed from adjacent atoms or from the terminal points of a four-atom system, unsaturated products are formed without rearrangement (e.g., olefin elimination), whereas if they are removed from the same atom or from a three-atom system, the formation of unsaturated products

[67] J., 1940, 899.   [68] J. Amer. Chem. Soc., 1940, 62, 933.
[69] See Ann. Reports, 1939, 36, 196.

involves rearrangement because the electrons required for stabilisation are not otherwise available; *e.g.*, the Hofmann and Lossen changes,

$$R\text{---}CO\text{---}NH\text{---}X \longrightarrow HX + CO\text{==}N\text{---}R$$
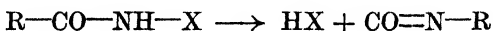
In these circumstances, dimerisation or cyclisation may occur instead of rearrangement. Removal from the ends of a five or six atom system usually leads to cyclisation as in the formation of γ-lactones from γ-halogeno-acids.

H. B. W.

4. FREE RADICALS.

(a) *Free Radicals of Long Life.*

To this class belong the comparatively stable radicals, the majority of which are structurally related to the triarylmethyls of Gomberg. Since radicals of this class were last reviewed [1] a large number of new radicals of the triarylmethyl type have been prepared and studied. These preparations follow, in general, the classical method of the action of a metal such as silver, copper, or mercury on a solution of the substituted methyl chloride in a solvent (benzene, toluene, or xylene) in an atmosphere of nitrogen or carbon dioxide. In some cases the free radicals are isolated, but in others the presence of the radical is usually indicated by the formation of the peroxide $Ar_3C\cdot O\cdot O\cdot CAr_3$. When the stability of the radical is low, the corresponding hexa-arylethane is isolated. Important additions to our knowledge have been made on the influence of constitution on radical stability, on methods for the detection and estimation of free radicals, and on the general theoretical aspects of the dissociation of molecules into pairs of neutral radicals. Particular attention may be drawn to the development of the use of measurements of magnetic susceptibility for the detection and estimation of radicals. The estimation of free radicals of the triarylmethyl type has also been effected by a study of the influence of the radicals on para-hydrogen.[2]

Hexa-arylethanes.—The small energy of dissociation of certain substituted ethanes into pairs of free radicals and the small bond strength of the carbon–carbon linkage in such compounds have been attributed, at least in part, to a stabilisation of the resulting radicals through resonance of the odd electron in the aromatic

[1] *Ann. Reports*, 1934, **31**, 240.
[2] G. M. Schwab and E. Agallidis, *Z. physikal. Chem.*, 1938, *B*, **41**, 59; G. M. Schwab and N. Agliardi, *Ber.*, 1940, **73**, 95.

nuclei.[3] The energy required to break the carbon–carbon bond in ethane is of the order of 85,000 cals. per mole. In the triphenylmethyl radical, the odd electron can be said to resonate among ten positions, namely, the ortho- and para-positions of each of the three phenyl groups and on the methyl carbon atom. This additional resonance energy amounts to about 38,000 cals. per mole and two such radicals stabilise the system by an amount (ca. 76,000 cals. per mole) sufficient to decrease the energy of dissociation to only a few thousand calories per mole and hence to give rise to dissociation (1—3% in benzene solution at 5°). In tri-4-diphenylylmethyl the odd electron can resonate among nineteen positions and in consequence the dissociation of the corresponding ethane is increased considerably (100% in benzene solution at 5°). These theories involve the fundamental assumption of a planar configuration for the triarylmethyl radical. Although E. S. Wallis and F. H. Adams [4] concluded that free radicals of this type cannot maintain a stable asymmetric configuration, G. Karagunis and G. Drikos [5] claim to have shown that both phenyl-p-tolyl-p-ethylphenylmethyl and phenyldiphenylyl-α-naphthylmethyl exist as mixtures of optical antipodes, which implies a non-planar configuration.[6] The existence of an optically active radical of this type would necessarily mean that the odd valency electron is capable of functioning like an atom or group in order to preserve the asymmetric configuration. The results of Karagunis and Drikos do not in themselves prove that the free triarylmethyl radicals are optically active, although they imply that the groups in the free radical are probably non-planar. It is also significant that attempts to prepare an optically active radical from a substituted methyl chloride of the type ArAr'Ar''CCl by the usual method do not appear to have met with any success. No further examples have been brought to light to substantiate the claims of Karagunis and Drikos.

In view of the important theoretical implications bound up with the spatial configuration of free radicals of the type ArAr'Ar''C further work on these lines will be awaited with interest. In the meantime it may be noted that C. S. Marvel, M. B. Mueller, and E. Ginsberg [7] have questioned the importance of resonance as a

[3] E. Hückel, Z. Physik, 1933, 83, 632; Trans. Faraday Soc., 1934, 30, 40; C. K. Ingold, ibid., p. 52; L. Pauling and G. W. Wheland, J. Chem. Physics, 1933, 1, 362; L. Pauling, Ch. XXII, "Organic Chemistry," Ed. by H. Gilman, John Wiley and Sons, Inc., New York, 1938.

[4] J. Amer. Chem. Soc., 1933, 55, 3838.

[5] Naturwiss., 1933, 21, 607; Z. physikal. Chem., 1934, B, 26, 428; Nature, 1933, 132, 354.

[6] See Ann. Reports, 1934, 31, 242.   [7] J. Amer. Chem. Soc., 1939, 61, 2008.

factor in influencing the dissociation of hexa-arylethanes. These workers have shown, from measurements of magnetic susceptibility, that tetraphenyldi-3-diphenylylethane (I) and tetraphenyldi-4-diphenylylethane (II) are dissociated to about the same extent in benzene solution at 25°, although the number of resonance forms in the diphenyl-3-diphenylyl radical is less than in the diphenyl-4-diphenylyl radical.

(I.)   (II.)
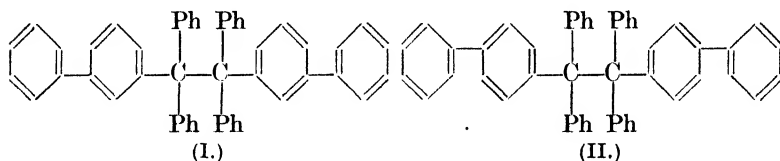
This result, coupled with the fact that hexa-3-diphenylylethane has been shown to be dissociated to the extent of 60%,[8] implies that the number of possible resonance forms in the free radical must play a rather minor part in determining the degree of dissociation of the hexa-arylethane. The following table correlates the number of resonance forms with the percentage dissociation of the hexa-arylethane in benzene solution for a series of related hydrocarbons :

Radical.	No. of resonance forms.	% Dissociation of hexa-arylethane.
Triphenylmethyl	10	2—3
Diphenyl-3-diphenylylmethyl	10	11—12
Tri-3-diphenylylmethyl	10	60
Diphenyl-4-diphenylylmethyl	13	13—14
Phenyldi-4-diphenylylmethyl	16	75
Tri-4-diphenylylmethyl	19	100

The importance of factors other than resonance on the dissociation of polyarylethanes has been discussed by C. B. Wooster[9] who claims that the heat of dissociation of s-tetraphenyldi-β-naphthylethane in solution does not agree with the value calculated on the basis of Pauling and Wheland's resonance theory. The nature of the carbon–carbon bond in hexa-arylethanes has also been discussed by H. E. Bent and his co-workers[10] with special reference to the significance of the effect of the resonance energy of the radical form.

S. T. Bowden and his collaborators have investigated the influence

      [8] C. S. Marvel, E. Ginsberg, and M. B. Mueller, J. Amer. Chem. Soc., 1939, 61, 77.
      [9] Ibid., 1936, 58, 2156.
      [10] H. E. Bent, G. R. Cuthbertson, M. Dorfman, and R. E. Leary, ibid., p. 165; H. E. Bent and G. R. Cuthbertson, ibid., p. 170; H. E. Bent and J. E. Cline, ibid., p. 1624.

of a variety of factors on the stability of radicals of the triaryl-methyl type in a series of papers which include many notable improvements in experimental technique. The phenoxyl group is shown to depress the radical stability, *i.e.*, the tendency of the substituted ethane to dissociate into a pair of radicals, when it replaces one phenyl group in triphenylmethyl. The thermal behaviour of diphenoxytetraphenylethane (III) shows that it is undissociated in boiling benzene solution. It does not give a coloured solution in liquid sulphur dioxide and is photochemically stable.

(III.) 2PhO—$\overset{\overset{\text{Ph}}{|}}{\underset{\underset{\text{Ph}}{|}}{\text{C}}}$—$\overset{\overset{\text{Ph}}{|}}{\underset{\underset{\text{Ph}}{|}}{\text{C}}}$—OPh $\longrightarrow$ 2PhO—$\overset{\overset{\text{Ph}}{|}}{\underset{\underset{\text{Ph}}{|}}{\text{C}}}$—OPh $+$ Ph$_2$C:CPh$_2$
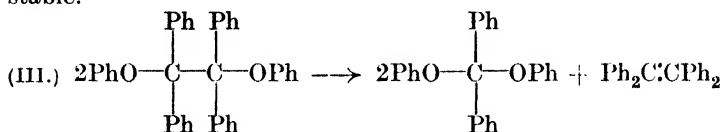
Colorations are produced in high-boiling solvents, which, however, are not reversible. These observations support Schmidlin's criticism [11] of Wieland's suggestion [12] that the colour changes are due simply to reversible thermal dissociation. It is shown that dissociation, quinonoidation and decomposition phenomena are all involved, and at elevated temperatures the ethane (III) is converted into diphenoxydiphenylmethane and tetraphenylethylene.[13] 2 : 2'-Dimethoxytriphenylmethyl (IV) is shown to be more stable than 2 : 4'-dimethoxytriphenylmethyl (V), which itself is much more stable than 2 : 4-dimethoxytriphenylmethyl (VI).[14] The radical stabilities, expressed as the percentage dissociation of the corre-

sponding ethane in 2% benzene solution, are considered to be in agreement with theoretical premises and with previous results of M. Gomberg and his co-workers,[15] who have shown that the introduction of one or more methoxyl groups into triphenylmethyl results in an increase in stability, although there appears to be no
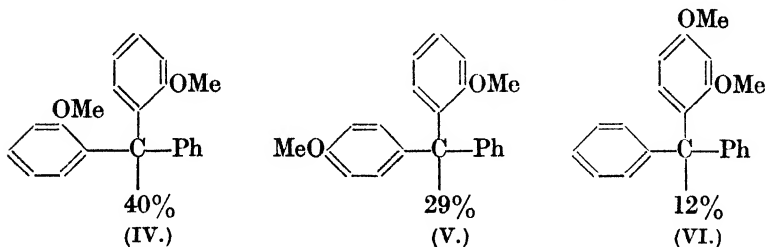
[11] "Das Triphenylmethyl," Stuttgart, 1914.
[12] *Ber.*, 1911, **44**, 2550. [13] S. T. Bowden, *J.*, 1939, 26.
[14] *Idem, ibid.*, p. 33.
[15] *J. Amer. Chem. Soc.*, 1923, **45**, 190, 207; 1925, **47**, 2373.

simple relationship between the stability of the radical and the number and position of the substituent methoxyl groups. 3 : 4-Methylenedioxytriphenylmethyl (VII) is less stable than 3 : 4-dimethoxytriphenylmethyl (VIII) [16] and p-methoxydiphenyl-4-diphenylylmethyl (IX) is considered to be more stable than the unsubstituted diphenyl-4-diphenylylmethyl, although a molecular weight determination on the former was not possible.

9%   22%   >15%
(VII.)   (VIII.)   (IX.)
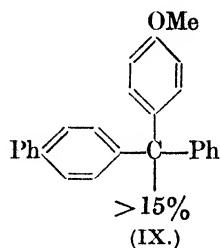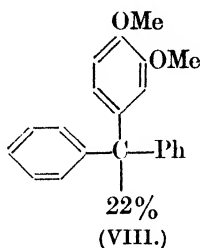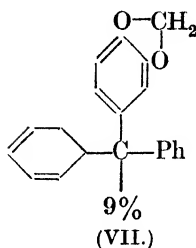
The study of the methyl-substituted triphenylmethyls has always proved troublesome owing to the tendency of the methyl substituents to promote internal instability in the radical systems.[17] A study of the effect of p-alkyl groups other than methyl on the dissociation of hexaphenylethane has been made by J. W. Copenhaver, M. F. Roy, and C. S. Marvel,[18] who prepared a series of triarylchloromethanes of general formula $(p\text{-}R\cdot C_6H_4)_3CCl$, where R = Et, n-Pr, isoPr, n-Bu, isoBu, and sec.-Bu, and showed that the colours of the solutions of the ethanes obtained from them by the action of metallic silver in toluene solution deepen with increase in weight of the substituent group R, thus indicating a progressive increase in dissociation. The relationship between colour and degree of dissociation is, however, not a simple one. As C. S. Marvel, M. B. Mueller, and E. Ginsberg [19] have pointed out, the colour of the free radical solution is in part a characteristic of the groups present and their positions and not of the degree of dissociation alone.[20] In this case, however, the deductions were later confirmed by M. F. Roy and C. S. Marvel,[21] who employed the magnetic method to determine the degree of dissociation of the series of hexa-p-alkylphenylethanes. The values thus obtained (for 0·1 molar solutions in benzene at 20°) are in the following

[16] S. T. Bowden, W. E. Harris, and D. I. Roberts, J., 1939, 302.
[17] M. Gomberg, Ber., 1904, 37, 1626.
[18] J. Amer. Chem. Soc., 1935, 57, 1311.
[19] Ibid., 1939, 61, 2008.
[20] Compare, inter alia, Anderson, ibid., 1935, 57, 1678.
[21] Ibid., 1937, 59, 2622.

table and show a small but progressive increase in dissociation with increase in molecular weight and branching of chain :

*Dissociation of Hexa-*p-*alkylphenylethanes,* $C_2(p\text{-}R\cdot C_6H_4)_6$.

R.	Colour of solution.	% Dissociation from magnetic susceptibility.	% Dissociation calc. from disproportionation.
Et	Orange	$3\cdot5 \pm 0\cdot3$	17 ± 2
n-Pr	Orange-red	$4\cdot2 \pm 0\cdot8$	21 ± 2
*iso*Pr	Orange-red	$4\cdot5 \pm 0\cdot6$	26 ± 2
n-Bu	Orange-red	$4\cdot9 \pm 0\cdot4$	—
sec.-Bu	Wine-red	$5\cdot9 \pm 0\cdot4$	33 ± 2
*iso*Bu	Wine-red	$6\cdot7 \pm 0\cdot4$	27 ± 2

Later work has shown that the values thus obtained for the radical stabilities of these tri-*p*-alkylphenylmethyls are probably too low owing to the tendency of the radicals to undergo further changes.

By means of measurements of magnetic susceptibility it has been shown by C. S. Marvel, W. H. Rieger, and M. B. Mueller [22] that, when purified tri-*p*-tolylchloromethane is shaken with metallic silver in benzene solution, an orange coloration is developed and at least 16% of the tri-*p*-tolylmethyl radical is present in a 0·08 molar solution at 30°, but after a short time the orange colour disappears and measurement of the magnetic susceptibility shows that the free radical is absent.   This is attributed to disproportionation of the radical to give tri-*p*-tolylmethane and a quinonoid hydrocarbon (X), which subsequently polymerises (with concomitant oxidation) to a colourless glass.[23]

$$2(p\text{-}Me\cdot C_6H_4)_3C\cdot \longrightarrow$$
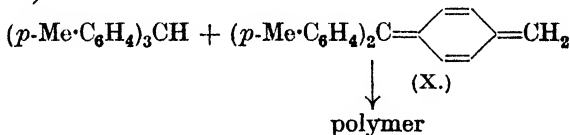
In similar manner radicals of the general formula $(p\text{-}R\cdot C_6H_4)_3C$, where $R = Et$, *n*-Pr, *iso*Pr, *sec.*-Bu, or *iso*Bu, are shown to undergo disproportionation to give $(p\text{-}R\cdot C_6H_4)_3CH$ and

$$(p\text{-}R\cdot C_6H_4)_2C{=}C_6H_4{=}CHR',$$
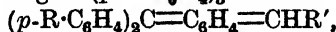
but in these cases decoloration does not occur, since the coloured quinonoid products do not polymerise.   By following the changes in magnetic susceptibility it is shown that the rates of disproportionation decrease with increase in molecular weight of R.[24] The order of increasing radical stability thus revealed agrees

[22] *J. Amer. Chem. Soc.*, 1939, **61**, 2769.

[23] Compare W. Schlenk and E. Meyer, *Ber.*, 1919, **52**, 8.

[24] C. S. Marvel, M. B. Mueller, C. M. Himel, and J. F. Kaplan, *J. Amer. Chem. Soc.*, 1939, **61**, 2771.

exactly with the order of increasing dissociation of the corresponding ethanes. This interpretation of the instability of the tri-p-tolyl-methyl and similar radicals is supported by the fact that tri-m-tolylmethyl, which cannot yield a quinonoid disproportionation product of the above type, is claimed to exist in the free radical form to an extent of not less than 40% and moreover it is stable in benzene solution. Further, the p-tert.-butylphenyldiphenylmethyl radical (XI) is stable, since it cannot give a quinonoid disproportionation product, whereas diphenyl-p-tolylmethyl (XII) and p-isopropylphenyldiphenylmethyl (XIII) are both capable of disproportionation, giving (XIV) and (XV) respectively together with the corresponding triarylmethanes, as in the cases of the tri-p-alkylphenylmethyl radicals mentioned above. The disproportionation reaction is thus obviously confined to those p-alkyl-triphenylmethyls in which the alkyl group has at least one hydrogen atom on the carbon atom adjacent to the ring.
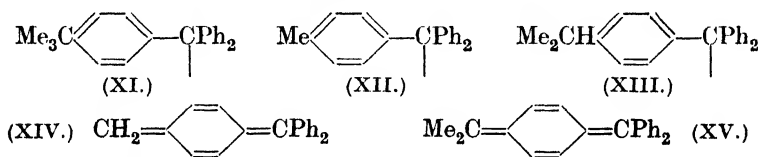
By using the data obtained on the rates of disproportionation of the radicals referred to above it was possible to calculate the degree of dissociation of the various ethanes at zero time and thus to obtain estimates of the effects of the various p-alkyl substituents. The values obtained in this way are incorporated in the above table and will be seen to be considerably greater than those resulting from the measurement of magnetic susceptibilities. These new results indicate that the magnetic susceptibility measurements were carried out on solutions in which the radicals had already suffered some disproportionation.

S. T. Bowden and D. L. Clarke [25] have prepared the diphenyl-o-tolylmethyl radical and shown that it has less tendency to isomerise than other methyltriphenylmethyls and is sufficiently stable to permit molecular weight determinations by the cryoscopic method, which showed that the stability is appreciably greater (ca. 20%) than that of triphenylmethyl. The same radical has also been prepared by C. S. Marvel, M. B. Mueller, C. M. Himel, and J. F. Kaplan,[26] who record a stability of $25 \pm 1\%$ and suggest that steric factors may contribute to this enhanced stability. The influence of methyl substituents in triphenylmethyl and its homopolar and ionised derivatives has also been studied by S. T. Bowden and

[25] *J.*, 1940, 883.　　　[26] *Loc. cit.* (ref. 24).

T. L. Thomas.[27] The introduction of a methyl group into the o-, m-, or p-position in one of the phenyl nuclei increases the basicity of the carbinol as well as the electrical conductivity of the triarylmethyl chloride in liquid sulphur dioxide (more effectively in the o- and p-positions than in the m-position). Molecular weight determinations show that the diphenyl-m-tolylmethyl (ca. 22%) and the 2 : 5-dimethyltriphenylmethyl (ca. 24%) radical also are more stable than triphenylmethyl. The changes due to isomerisation and disproportionation to which radicals of this type are susceptible have been investigated by Bowden and Thomas by the use of photoelectric and tintometric methods specially devised to record small changes in the colours of the systems. These methods indicate that isomerisation is slow with triphenyl-, diphenyl-o-tolyl-, and 2 : 5-dimethyltriphenyl-methyl, more rapid with diphenyl-m-tolylmethyl, and much more rapid with diphenyl-p-tolylmethyl.

Free radicals of the triarylmethyl type containing chlorine, bromine, or iodine in one or more of the phenyl groups have been previously investigated by M. Gomberg and his co-workers [28] and have been shown to possess certain peculiar features which rendered difficult both their isolation and the determination of their molecular weights by the usual cryoscopic methods. The abnormal properties of these radicals are due, at least in part, to the reactivity of the nuclear-substituted halogen atom towards metallic silver with formation of a new secondary radical. S. T. Bowden and T. F. Watkins [29] have investigated the reactivity of fluorine in triphenyl-methyl fluoride and in p-fluorotriphenylmethyl. A priori consideration would suggest that the factors leading to the formation of a secondary radical would be much less evident in the fluoro-substituted radical owing to the lower polarisability of the fluorine atom and its low reactivity in triphenylmethyl fluoride, which has been shown by F. F. Blicke [30] to be remarkably stable to molecular silver. Agitation of the freshly prepared p-fluorotriphenylmethyl radical, prepared in the normal manner from p-fluorotriphenyl-methyl chloride, with molecular silver, however, led to a partial removal of the nuclear fluorine atom with formation of the secondary radical. This behaviour indicates that the halogen atom in the aromatic C–F linkage of the free radical is more reactive than that in the aliphatic C–F linkage in triphenylmethyl fluoride, whereas the opposite is true for the corresponding C–Br linkages. The formation of the secondary radical, which is regarded as existing

[27] J., 1940, 1242.
[28] Ber., 1904, **37**, 1626; 1906, **39**, 3274; J. Amer. Chem. Soc., 1923, **45**, 1765.
[29] J., 1940, 1249.   [30] J. Amer. Chem. Soc., 1924, **46**, 1515.

in quinonoid and benzenoid modifications (XVI and XVII), may for simplicity be represented as follows, although it is more than probable that the reaction proceeds through a unimolecular quinonoid intermediate :

$$F\!\!-\!\!\overset{\overset{\displaystyle Ph}{|}}{\underset{\underset{\displaystyle Ph}{|}}{C}}\!\!-\;+\;Ag\;+\;F\!\!-\!\!\overset{\overset{\displaystyle Ph}{|}}{\underset{\underset{\displaystyle Ph}{|}}{C}}\!\!-\;\longrightarrow$$

$$F\!\!-\!\!\overset{\overset{\displaystyle Ph}{|}}{\underset{\underset{\displaystyle Ph}{|}}{C}}\!\!=\!\!CPh_2 \;\; \rightleftharpoons \;\; F\!\!-\!\!\overset{\overset{\displaystyle Ph}{|}}{\underset{\underset{\displaystyle Ph}{|}}{C}}\!\!-\!\!\overset{\overset{\displaystyle Ph}{|}}{\underset{\underset{\displaystyle Ph}{|}}{C}}\!\!-$$

(XVI.)   (XVII.)
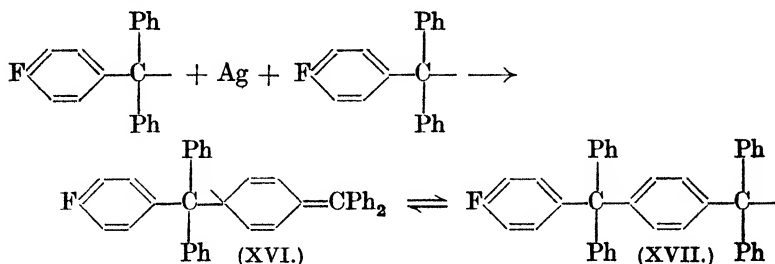
Similar reactivity of the p-fluorine atom in triphenylmethyls, giving rise to the formation of secondary radicals, has been recorded by F. Bacon and J. H. Gardner,[31] who have also shown that mono-, di-, and tri-p-fluorotriphenylmethyl chlorides rearrange in liquid sulphur dioxide to yield chloro- and fluorochloro-triphenylmethyl fluorides.

It is well known that, whereas hexaphenylethane is dissociated in benzene solution to the extent of only a few units %, replacement of the six phenyl groups by the six larger 4-diphenylyl groups increases the dissociation to 100%. Numerous hexa-arylethanes containing other large aromatic and hydroaromatic nuclei have recently been prepared. 4 : 4′-Dibenzoyltriphenylmethyl has been shown to exist to the extent of 36% in benzene solution in equilibrium with its dimeride.[32]   J. H. Brown and C. S. Marvel [33] prepared a hexacyclohexylphenylethane regarded as the p-isomeride, but later work showed it to be a mixture of the o-, m-, and p-isomerides.[34]   C. S. Marvel and C. H. Himel (loc. cit.) prepared di-p-cyclohexylphenyltetraphenylethane,   tetra - p - cyclohexylphenyldi-phenylethane and hexa-p-cyclohexylphenylethane, which, on the basis of measurements of their magnetic susceptibility, dissociate in benzene solution at 25° to the extent of $9 \pm 1\%$ (in 0·1 M-solution), $10 \pm 1\%$ (in 0·1M-solution), and $50 \pm 7\%$ (in 0·01M-solution) respectively.   The last value corresponds to a dissociation of about 22% in 0·08M-concentration, which is very close to that found for the hexa-p-alkylphenylethanes calculated from the rates of disproportionation.   It is suprising that the dissociations of the di- and the tetra-substituted compounds are almost identical.

[31] J. Org. Chem., 1938, 3, 281.
[32] E. Connerade, Bull. Soc. chim. Belg., 1936, 45, 647.
[33] J. Amer. Chem. Soc., 1937, 59, 1175.
[34] C. S. Marvel and C. H. Himel, ibid., 1940, 62, 1550.

Replacement of the phenyl group by the *p-cyclo*hexylphenyl group thus results in a small but appreciable increase in dissociation which is not comparable with the large increase resulting from the replacement of phenyl by the 4-diphenylyl group. Such a result is to be anticipated on the basis of the resonance theory. *s*-Di-*p-cyclo*hexylphenyltetraphenylethane has also been prepared by I. Zugrăvescu and S. Zugrăvescu,[35] who observed the red coloration due to the *p-cyclo*hexyltriphenylmethyl radical.

Diphenyl-3-acenaphthylmethyl (XVIII) has been shown by S. T. Bowden and W. E. Harris [36] to possess a radical stability of the same order as diphenyl-α-naphthylmethyl (XIX),[37] but whereas the thermal decomposition of diphenyl-α-naphthylmethyl formate

(XVIII.)   70%   60%   (XIX.)
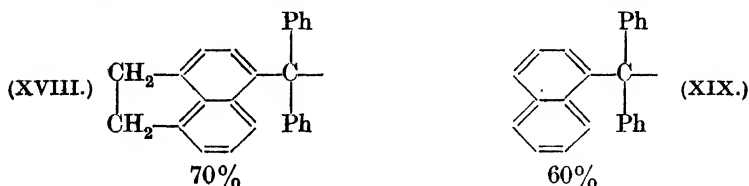
occurs at 99° with formation of carbon dioxide and diphenyl-α-naphthylmethane, diphenyl-3-acenaphthylmethyl formate gives neither carbon dioxide nor the methane under similar conditions. E. Müller and W. Kruck [38] have shown that, in agreement with quantum-theoretical views, the introduction of large groups such as chrysyl and phenanthryl increases the ability of the hexa-arylethane to dissociate. For example, ααββ-tetraphenyl-di-2-chrysylethane is dissociated to the extent of at least 65% in naphthalene at 125°. However, it is pointed out that the accumulation of substituents occupying the largest possible space should eventually result in a decreased ability to dissociate because the planar configuration of the substituents around the central carbon atom is rendered more difficult or impossible. Hexa-arylethanes containing the phenanthrene nucleus have been studied by W. E. Bachmann and M. C. Kloetzel,[39] who have shown that the radicals 1-, 2-, and 3-phenanthryldiphenylmethyl are relatively stable in the dark, whereas both 9-phenanthryldiphenylmethyl and 9-phenanthryldiphenylenemethyl decompose spontaneously. The degree of dissociation of these hexa-arylethanes, calculated from molecular weight determinations, shows that the dissociation-promoting

[35] *Bul. Soc. Chim. Română*, 1937, **19**, 85.

[36] *J.*, 1939, 307.

[37] Compare W. Schlenk and J. Renning, *Annalen*, 1912, **394**, 193; M. Gomberg and C. S. Schoepfle, *J. Amer. Chem. Soc.*, 1919, **41**, 1655; W. E. Bachmann and M. C. Kloetzel, *J. Org. Chem.*, 1937, **2**, 356.

[38] *Ber.*, 1938, **71**, 1778.   [39] *J. Org. Chem.*, 1937, **2**, 356.

effects of 1- and 2-phenanthryl rank with that of α-naphthyl and are greater than that of 4-diphenylyl and 3-phenanthryl, which itself is greater than that of β-naphthyl. The two 9-phenanthryl derivatives were found, in agreement with E. Müller and W. Kruck,[40] to be too unstable to permit molecular weight determinations to be carried out.

Tetra-arylethanes.—W. T. Nauta, D. Mulder, and their collaborators have examined the behaviour of a number of symmetrical tetra-arylethanes with the object of obtaining stable diarylmethyl radicals. Phenylethane, αβ-diphenylethane and ααβ-triphenylethane are very stable hydrocarbons in which the ethane carbon–carbon linkage shows no evidence of weakness. *s*-Tetraphenylethane can be distilled at 280° without decomposition, but an incipient weakening of the carbon–carbon bond is revealed in its reaction with metallic potassium, which results in a cleavage : $Ph_2CH \cdot CHPh_2 + 2K \rightarrow 2Ph_2CHK$. The diphenylmethyl radical is probably one of intermediate stability between those of the triarylmethyl type and those of short life discussed in section (*b*). In pentaphenylethane the carbon–carbon bond is weakened still further, as shown by its cleavage with sodium–potassium alloy and with hydriodic acid and phosphorus as well as by its dissociation on heating.

W. T. Nauta and P. J. Wuis [41] have shown that dimesitylchloromethane gives evidence of radical formation when it is heated with metallic silver in benzene solution in absence of oxygen. A deep red-violet coloration was formed which was destroyed by oxygen, but the dimeric tetramesitylethane was not isolated.[42] On the other hand *s*-tetra-α-naphthylethane develops no colour in benzene solution and is completely undissociated.[43] *s*-Tetra-*p*-methoxyphenylethane shows a similar behaviour and develops no colour when heated alone or in xylene solution.[43a] It is suggested, however, that diarylmethyl radicals are formed as transient intermediates during the preparation of the tetra-arylethanes.[44] Colorations are frequently observed during the reaction of the halide with metallic silver and it is significant that, if the reaction with diphenylchloromethane is carried out in an atmosphere of oxygen or nitrous oxide, the yield of *s*-tetraphenylethane is reduced from 100 to 2—8%, presumably owing to the removal of the unstable diphenylmethyl radicals by means of oxygen as a peroxide.[45] The products obtained

[40] *Loc. cit.* (ref. 38).   [41] *Rec. Trav. chim.*, 1937, **56,** 535.

[42] *Idem, ibid.*, 1938, **57,** 41.

[43] P. J. Wuis and D. Mulder, *ibid.*, p. 1385.

[43a] W. T. Nauta and D. Mulder, *ibid.*, 1939, **58,** 1062.

[44] *Idem, ibid.*, p. 514.   [45] *Idem, ibid.*, p. 1070.

by the action of oxygen on diarylmethyl radicals have been reviewed by W. T. Nauta, P. J. Wuis, and D. Mulder,[46] who conclude that stable free radicals of the type Ar_2CH are not obtained when the aryl groups are unsubstituted but that when all the ortho-positions are substituted the diarylmethyl radical has properties similar to those of unsubstituted triphenylmethyl.

An indication of the existence of a free radical of the type R_2CH has been provided by G. Wittig and B. Obermann,[47] who obtained evidence that s-tetra-(ββ-diphenylvinyl)ethane (XX) dissociates into a pair of radicals, thus :

$$(XX.) \quad \begin{matrix} Ph_2C\!:\!CH\cdot CH\cdot CH\!:\!CPh_2 \\ Ph_2C\!:\!CH\cdot CH\cdot CH\!:\!CPh_2 \end{matrix} \longrightarrow 2(Ph_2C\!:\!CH)_2CH$$
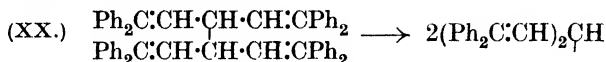
This example is of particular interest, since the methyl carbon atom of the radical is not attached directly to an aromatic group. The evidence upon which the claim is made consists in (a) proof of the absence of a conjugated system by a negative Diels–Alder reaction, (b) formation of a yellow-green colour in boiling xylene or anisole solution, which disappears on cooling, and (c) facile reduction with hydriodic acid and phosphorus in boiling glacial acetic acid solution to $1 : 1 : 5 : 5$-tetraphenyl-n-pentane. The corresponding hexa-(ββ-diphenylvinyl)ethane (XXII) was later examined by G. Wittig and H. Kosack,[48] who observed that, whereas s-tetradiphenylylethane is stable at 300°, both hexa-(ββ-diphenylvinyl)ethane (XXII) and s-diphenyltetra-(ββ-diphenylvinyl)ethane (XXI) exist mainly in the radical form. The stability of the free radicals is shown to follow the order $Ph_2C\!:\!CH\cdot CPh_2 < (Ph_2C\!:\!CH)_2CPh < (Ph_2C\!:\!CH)_3C$. Free radicals are not formed if the vinyl groups can undergo the allylic rearrangement.[49]

$$\begin{matrix} Ph\diagdown \quad \diagup Ph \\ Ph_2C\!:\!CH\!\!\rightarrow\!C\cdot C\!\!\leftarrow\!\!CH\!:\!CPh_2 \\ Ph_2C\!:\!CH\diagup \quad \diagdown CH\!:\!CPh_2 \\ (XXI.) \end{matrix} \qquad \begin{matrix} Ph_2C\!:\!CH\diagdown \quad \diagup CH\!:\!CPh_2 \\ Ph_2C\!:\!CH\!\!\rightarrow\!C\cdot C\!\!\leftarrow\!\!CH\!:\!CPh_2 \\ Ph_2C\!:\!CH\diagup \quad \diagdown CH\!:\!CPh_2 \\ (XXII.) \end{matrix}$$
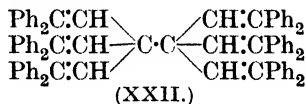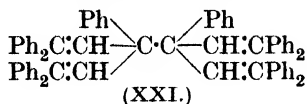
Penta-arylethanes.—With both s-tetra-arylethanes and hexa-arylethanes dissociation gives rise to two radicals of similar type, but with the penta-arylethanes two different radicals, often of widely different stability, result. A study of the penta-arylethanes is therefore likely to provide many points of special interest. Such a study has been made by W. E. Bachmann and F. Y. Wiselogle,[50] who prepared a complete series of the twelve penta-arylethanes

[46] *Chem. Weekblad*, 1940, **37**, 96.   [47] *Ber.*, 1935, **68**, 2214.
[48] *Annalen*, 1937, **529**, 167.
[49] Compare C. S. Marvel, M. B. Mueller, and W. J. Peppel, *J. Amer. Chem. Soc.*, 1938, **60**, 410.
[50] *J. Org. Chem.*, 1936, **1**, 354.

containing (*a*) five phenyl groups, (*b*) four phenyl and one 4-diphenylyl group, (*c*) three phenyl and two 4-diphenylyl groups, (*d*) two phenyl and three 4-diphenylyl groups, (*e*) one phenyl and four 4-diphenylyl groups, and (*f*) five 4-diphenylyl groups. The temperatures at which these penta-arylethanes first become coloured in ethyl benzoate solution owing to dissociation into radicals are recorded below and the results indicate that successive replacement of phenyl by 4-diphenylyl progressively weakens the ethane carbon–carbon bond. The colours produced on dissociation are those due to the free triarylmethyl radicals only and the twelve compounds thus fall into four groups as indicated in the table. Cleavage of the penta-arylethane by means of sodium amalgam also indicates that an increase in the number of 4-diphenylyl groups reduces the resistance of the carbon–carbon bond to scission.

Temperatures at which Colour develops in Ethyl Benzoate Solution.

Penta-arylethane, $R_3C\cdot CHR_2$.	Temp.	Colour.	Radical.
Pentaphenylethane	105°	Yellow	Ph_3C
2-Diphenylyltetraphenylethane	92	,,	,,
2 : 2-Didiphenylyltriphenylethane	90	,,	,,
1-Diphenylyltetraphenylethane	88	Orange-red	$p\text{-}Ph\cdot C_6H_4\cdot CPh_2$
1 : 2-Didiphenylyltriphenylethane	88	,,	,,
1 : 2 : 2-Tridiphenylyldiphenylethane ...	80	,,	,,
1 : 1-Didiphenylyltriphenylethane	83	Light-red	$(p\text{-}Ph\cdot C_6H_4)_2CPh$
1 : 1 : 2-Tridiphenylyldiphenylethane ...	83	,,	,,
1 : 1 : 2 : 2-Tetradiphenylylphenylethane	82	,,	,,
1 : 1 : 1-Tridiphenylyldiphenylethane ...	81	Dark-red	$(p\text{-}Ph\cdot C_6H_4)_3C$
1 : 1 : 1 : 2-Tetradiphenylylphenylethane	78	,,	,,
Pentadiphenylylethane	71	,,	,,

(For purposes of abbreviation the carbon atoms are numbered thus :

$$R_3\overset{1}{C}\cdot\overset{2}{C}HR_2.)$$

The triarylmethyl radicals are much more stable than the diarylmethyl radicals and hence when 1-diphenylyltetraphenylethane, for example, is refluxed at 213° in ethyl benzoate solution some *s*-tetraphenylethane is formed by the irreversible combination of the resulting diphenylmethyl radicals, thus :

Similar results were obtained with pentaphenylethane and with penta-4-diphenylylethane. Further, solutions of the penta-arylethanes absorb oxygen rapidly at 80—105°, the main products

being the unsymmetrical peroxides $R_3C \cdot O \cdot O \cdot CHR_2$, which are formed through the agency of the free radicals $R_3C \cdot$ and $R_2HC \cdot$. The energy of activation for the dissociation of pentaphenylethane is 27·6 kg.-cals., the values for ethane and hexaphenylethane being 80 and 19 respectively. The rates of dissociation of the penta-arylethanes have been measured by W. E. Bachmann and G. Osborn [51] by estimating the rate of absorption of iodine in a solvent in presence of ethyl alcohol and pyridine. The products are the triarylmethyl ethyl ether and the diarylmethylpyridinium iodide, thus :

$$Ar_3C \cdot CHAr_2 + EtOH + C_5H_5N + I_2 \longrightarrow$$
$$Ar_3C \cdot OEt + C_5H_5N {<}^{CAr_2H}_{I} + HI$$
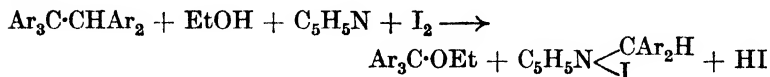
The results, which are in good agreement with those previously obtained by W. E. Bachmann and F. Y. Wiselogle [52] on oxygen absorption, show that the rate-controlling stage is a first-order reaction corresponding with a unimolecular process of dissociation. Determinations of the rate constant and half-life periods of aryl-tetraphenylethanes of the type $Ph_3C \cdot CHPhR$ show that dissociation is most rapid when R = 9-phenanthryl, α-naphthyl, and 2-fluorenyl, the 4-diphenylyl and p-methoxyphenyl groups have an intermediate value, and the p-tolyl and phenyl groups are least effective.

Magnetic Susceptibility.—The measurement of magnetic susceptibility has proved to be of great value in the investigation of the chemistry of free radicals. Molecules which possess an odd number of electrons contain one which is magnetically non-compensated and are highly paramagnetic.[53] It has been calculated that the presence of one such electron should lead to a paramagnetic susceptibility of 1260 ($\times 10^{-6}$) units at room temperature. Tri-4-diphenylylmethyl, both in the solid form and in solution, gives a value of 1200 units [54] and is therefore unassociated.

The method involves a measurement of the magnetic susceptibility of, for example, a hexa-arylethane, from which the molecular susceptibility is calculated. A comparison of the observed value with that calculated on the basis of Pascal's diamagnetic atomic susceptibilities gives the paramagnetic contribution of that part of the molecule which is dissociated. The degree of dissociation of the ethane is the ratio of the observed paramagnetic contribution to that which would be expected if dissociation were complete. Since the paramagnetic susceptibility is determined as a correction of the experimental diamagnetism (which involves certain assump-

[51] *J. Org. Chem.*, 1940, **5**, 29.   [52] *Ibid.*, 1936, **1**, 354.

[53] N. W. Taylor, *J. Amer. Chem. Soc.*, 1926, **48**, 854.

[54] E. Müller, I. Müller-Rodloff, and W. Bunge, *Annalen*, 1935, **520**, 235.

tions and experimental difficulties), the observed paramagnetic values should show at least 2% dissociation to be significant.

Extensive application of the measurement of magnetic susceptibilities to the elucidation of problems connected with the existence and stability of free radicals has been made by E. Müller and his collaborators. It has been shown that diphenyl-3 : 3'-bis-diphenylmethyl (XXIII) exists as a true diradical to the extent of 1% at room temperature and 6 ± 2% at 74° in benzene solution, whereas the isomeric diphenyl-4 : 4'-bisdiphenylmethyl (XXIV), both in the solid state and in benzene solution, appears to exist in the quinonoid form (XXV). Such a quinonoid form is, of course, not possible in the case of the 3 : 3'-isomeride.[55] The corresponding 4 : 4''-diradical in the *p*-terphenyl series, *p*-terphenyl-4 : 4''- bisdiphenylmethyl (XXVI), has also been prepared in solution by E. Müller and G. Sok,[56] but measurements of its magnetic susceptibility have not been reported. A number of other diradicals which

(XXIII.)   (XXIV.)

(XXV.)   (XXVI.)
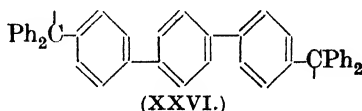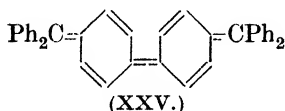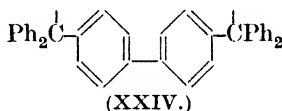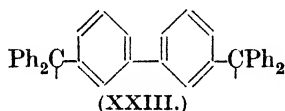
are capable of reverting to a quinonoid form were also examined. These were all shown to exist substantially in the quinonoid form and it was therefore inferred that the existence of such paramagnetic diradicals is only possible when the passage into a valency-tautomeric quinonoid system cannot take place.[57] The interesting discovery was subsequently made that 4 : 4'-diradicals in the diphenyl series can exist provided that the ortho-positions are suitably substituted. E. Müller and H. Neuhoff [58] have prepared the free diradical

(XXVII.)   (XXVIII.)
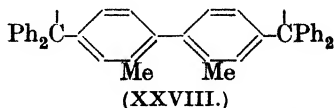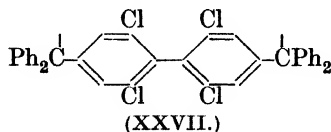
2 : 6 : 2' : 6'-tetrachlorodiphenyl-4 : 4'-bisdiphenylmethyl (XXVII), which shows about 17% dissociation at room temperature and

[55] E. Müller and I. Müller-Rodloff, *Annalen*, 1935, **517**, 134.
[56] *Ber.*, 1937, **70**, 1990.
[57] E. Müller and I. Müller-Rodloff, *Ber.*, 1935, **68**, 1276; E. Müller and W. Wiesemann, *Ber.*, 1936, **69**, 2157; E. Müller and W. Bunge, *ibid.*, p. 2164.
[58] *Ber.*, 1939, **72**, 2063.

about 28% at 80° in solution. In its chemical and physical pro-
perties this diradical appears to behave as a triarylmethyl of double
function, each half of the molecule behaving as if the other half
were not present. The stability of the diradical form in this type
of molecule, in contrast to the instability of the corresponding
chlorine-free compound (XXIV), is attributed to the non-planar
configuration imposed on the molecule by the presence of the
o-substituents, which prevents a reversion to a quinonoid form.
E. Müller and E. Tietz [59] have also shown that $2 : 6 : 2' : 6'$-tetra-
chlorodiphenyl - 4 : 4' - bis - 4'' - diphenylylphenylmethyl   (XXIX)
exists partly as a diradical, the stability of which is attributed to

(XXIX.)
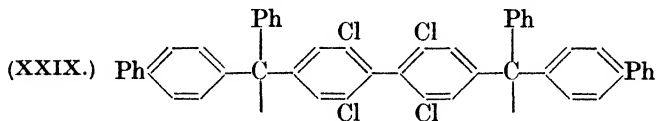
hindrance to free rotation at the central C_1–$C_{1'}$ bond imposed by the
o-substituents, and, as with the simple triarylmethyls, replacement of
phenyl by 4-diphenylyl results in an increase in the degree of dissoci-
ation.   A further example of a stable 4 : 4'-diradical in the diphenyl
series has been provided by W. Theilacker and W. Ozegowski,[60] who
prepared $2 : 2'$-dimethyldiphenyl-4 : 4'-bisdiphenylmethyl (XXVIII).
Their theoretical interpretation of these results differs somewhat
from that of Müller and Neuhoff, but for further details the original
papers should be consulted.

From these results the important conclusion can be drawn that
when both tervalent carbon atoms in the diradical are in 4 : 4'-
positions in the diphenyl system the compounds are diamagnetic,
whereas the corresponding 3 : 3'-isomerides are paramagnetic like
radicals containing one tervalent carbon atom, but in compounds
of the diphenyl type with a non-planar configuration due to the
presence of ortho-substituents paramagnetic properties are shown
even if both tervalent carbon atoms are attached to the 4 : 4'-
positions.   These conclusions find a close parallel in the measure-
ments of absorption spectra described by L. W. Pickett, G. F.
Walter, and H. France,[61] who have shown that diphenyl derivatives
with restricted rotation differ markedly in the form and intensity
of their absorption spectra from those capable of free rotation.[62]

Reference may be made here to the preparation of a radical of
potential triple triarylmethyl function (XXX) by the action of
either phenyl-lithium or phenylmagnesium bromide on 4 : 4'-di-

[59] Naturwiss., 1940, 28, 189.   [60] Ber., 1940, 73, 33.
[61] J. Amer. Chem. Soc., 1936, 58, 2296.
[62] Compare A. E. Gillam and D. H. Hey, J., 1939, 1170.

benzoylbenzophenone, conversion of the resulting triol into the trichloride, and subsequent treatment with metallic silver.[63]   In view of its properties and the fact that E. Müller and I. Müller-Rodloff have found that diphenyl-4 : 4'-bisdiphenylmethyl (XXIV) exists largely in the quinonoid form, it is considered that this compound exists mainly in the quinonoid form (XXXI), which, however, still retains one tervalent carbon atom.

(XXX.)   (XXXI.)   (XXXII.)
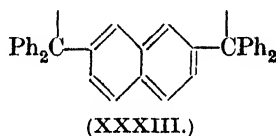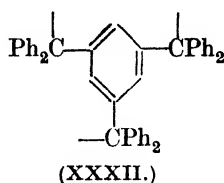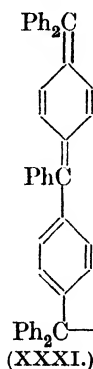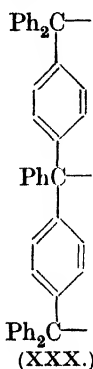
(XXXIII.)

Radicals with more than one tervalent carbon atom have also been prepared by M. Leo,[64] who, by the action of copper powder on 1 : 3 : 5-trichlorobenzhydrylbenzene, obtained the corresponding free radical (XXXII), which appeared to be mainly unimolecular in solution.   The properties of this radical are abnormal in many respects and it is suggested that the free valencies saturate one another to some extent within the molecule.   A similar compound (XXXIII) was derived from 2 : 7-dichlorobenzhydrylnaphthalene. Both of these radicals resemble in some respects the *m*-diradicals of W. Schlenk and M. Brauns,[65] of which diphenyl-3 : 3'-bisdiphenylmethyl (XXIII) is typical, in which the development of a quinonoid system is not possible.

Magnetic measurements have also been carried out on a variety of other compounds which have been claimed or suspected as free radicals.   Among compounds which have shown no evidence of a free radical form is the coloured dimeric keten of W. Langenbeck and

(XXXIV.) $\begin{array}{c} Ph_2C\!-\!\!-\!CPh_2 \\ CO\!-\!\!-\!CO \end{array}$ $-CPh_2 \cdot CO \cdot CO \cdot CPh_2-$ (XXXV.)

H. Langenbeck,[66] which was regarded as 3 : 3 : 4 : 4-tetraphenyl-*cyclo*butane-1 : 2-dione (XXXIV) and might therefore give rise to

[63] E. Connerade, *Bull. Soc. chim. Belg.*, 1937, **46**, 179.
[64] *Ber.*, 1937, **70**, 1691.   [65] *Ber.*, 1915, **48**, 661, 716.
[66] *Ber.*, 1928, **61**, 938.

the diradical (XXXV).[67] F. L. Allen and S. Sugden,[68] however, have drawn attention to the fact that the magnetic method is not decisive in the case of diradicals, since, if the two free electrons have opposed spins, no paramagnetism would result. Negative results have been obtained for the potassium derivatives of 2 : 6-dimethylpyrone, 2-methylchromone, and 2 : 3 : 6 : 7-dibenzoxanthone, which exclude the possibility of formulating these compounds as free radicals of the ketyl type.[69] Negative results were also obtained by F. L. Allen and S. Sugden [70] for 10 : 10'-bis-5 : 10-dihydrophenarsazine and thiobenzophenone. In the latter case, as also in that of pp'-bisdimethylaminothiobenzophenone,[71] two free electrons are present and if their spins are opposed no paramagnetism would result. Measurements of the magnetic susceptibilities of a series of $\omega\omega'$-phenylpolyenes show a constant paramagnetic increment of $10 \cdot 6 \times 10^{-6}$, which is independent of temperature.[72] The theoretical significance of this result is discussed by the authors and it is concluded that on the evidence available diradicals are unlikely to be responsible for this increment.

Positive results have been obtained from magnetic measurements on pentaphenyl*cyclo*pentadienyl, which indicate a monomeric radical.[73] The existence of free radicals has also been confirmed in a number of other cases, including $\alpha\alpha$-diphenyl-β-trinitrophenyl-hydrazyl, tri-4-diphenylylmethyl, and tri-p-nitrophenylmethyl.[74] As a result of measurements on hexaphenylethane itself [75] it is shown that the magnetic method is best suited to compounds which are highly dissociated, or alternatively to high concentrations of compounds which are slightly dissociated. With hexaphenylethane the concentration should not be below 4%, at which strength a dissociation of 2·1% at 20° was revealed.

Tetra-arylhydrazines.—In the same way that the successive substitution of phenyl groups for the hydrogen atoms of ethane weakens the ethane carbon–carbon bond, substitution of aryl groups for the hydrogen atoms of any simple dimeric molecule might be expected to result in a similar weakening of the central bond. Many reactions of the tetra-arylhydrazines, $Ar_2N \cdot NAr_2$, have been attributed to preliminary dissociation into the free radicals $Ar_2N \cdot$. C. K. Cain

[67] E. Müller, *Ber.*, 1935, **68**, 1883.   [68] *J.*, 1936, **440**.
[69] E. Müller and F. Teschner, *Annalen*, 1936, **525**, 1.
[70] *Loc. cit.*
[71] E. Müller and I. Müller-Rodloff, *Ber.*, 1935, **68**, 1276.
[72] E. Müller and I. Dammerau, *Ber.*, 1937, **70**, 2561.
[73] E. Müller and I. Müller-Rodloff, *Ber.*, 1936, **69**, 665.
[74] E. Müller, I. Müller-Rodloff, and W. Bunge, *Annalen*, 1935, **520**, 235; F. L. Allen and S. Sugden (ref. 68).
[75] E. Müller and I. Müller-Rodloff, *Annalen*, 1936, **521**, 89.

and F. Y. Wiselogle [76] have recently investigated the dissociation of tetraphenylhydrazine by a study of the kinetics of its reaction with nitric oxide between 75° and 100° and have shown that, under certain experimental conditions, dissociation into free diphenylnitrogen radicals, $Ph_2N \cdot NPh_2 \longrightarrow 2Ph_2N\cdot$, is the primary rate-controlling stage. These results provide a close parallel to those previously obtained by K. Ziegler, Ph. Orth, and K. Weber [77] for the reaction between hexaphenylethane and nitric oxide at 0°. The energy of activation for the dissociation of tetraphenylhydrazine is given as 30 ± 1.5 kg.-cals., which is 10 kg.-cals. greater than the energy of dissociation of unsubstituted hydrazine calculated from thermochemical data. This is in sharp contrast to the known lowering of bond-strength and activation energy by the substitution of phenyl groups for hydrogen atoms in the ethane series. It appears, therefore, that if the substitution of an aryl group for a hydrogen atom in hydrazine decreases the bond strength, then the energy of activation for the union of two bivalent nitrogen radicals must be excessively high. In order to obtain further information on this point the determination of the energy of dissociation of tetraphenylhydrazine will be awaited with interest.

It has not been possible to include in this Report an account of recent work on the ketyls or on free radicals of the semiquinone type which are involved in reversible two-step oxidation processes. Reference may be made to the application of the magnetic method to the study of the ketyl radicals obtained by the action of alkali metals on anhydrous ketones such as benzophenone.[78] Semiquinone radicals have been reviewed elsewhere by L. Michaelis,[79] and again by L. Michaelis and M. P. Schubert.[80]

(b) Free Radicals of Short Life.

Theories involving the participation of free radicals of short life in chemical reactions are attractive from their very simplicity, but

[76] J. Amer. Chem. Soc., 1940, **62**, 1163.   [77] Annalen, 1933, **504**, 131.

[78] S. Sugden, Trans. Faraday Soc., 1934, **30**, 18; R. N. Doescher and G. W. Wheland, J. Amer. Chem. Soc., 1934, **56**, 2011; F. L. Allen and S. Sugden, J., 1936, 440; E. Müller and F. Teschner, Annalen, 1936, **525**, 1; E. Müller and W. Wiesmann, ibid., 1937, **532**, 116; 1939, **537**, 86; E. Müller and W. Janke, Z. Elektrochem., 1939, **45**, 380.

[79] Chem. Reviews, 1935, **16**, 243.

[80] Ibid., 1938, **22**, 437; see also, inter alia, G. Schwarzenbach and L. Michaelis, J. Amer. Chem. Soc., 1938, **60**, 1667; L. Michaelis, M. P. Schubert, R. K. Reber, J. A. Kuck, and S. Granick, ibid., p. 1678; L. Michaelis, M. P. Schubert, and S. Granick, ibid., 1939, **61**, 1981; S. Granick, L. Michaelis, and M. P. Schubert, ibid., 1940, **62**, 1802; J. Weiss, Chem. and Ind., 1938, 517.

unless the existence of radicals can be proved experimentally such theories should be accepted with due reservation. In the gaseous phase the detection of radicals of short life is usually straightforward, but in the case of reactions in solution the problem presents greater difficulties and more reliance has to be placed on accumulated evidence of a circumstantial character. Until recently few attempts had been made to bridge the gap between the radicals of long life and those of short life. The distinction between these two types is apparent rather than real and it is probable that the sequence methyl, phenylmethyl, diphenylmethyl, and triphenylmethyl represents a gradual transition. The work of W. T. Nauta and D. Mulder and their collaborators on diarylmethyls reported in section (a), and the investigations of S. T. Bowden [81] and of S. T. Bowden, D. L. Clarke, and W. E. Harris [82] on the behaviour of carbinols and their derivatives containing the groups CH_3, CH_2Ph, $CHPh_2$, and CPh_3 represent attempts to elucidate the behaviour of radicals of intermediate stability. The occurrence of free radicals of short life in reactions both in the gaseous phase and in solution has been reviewed by G. Wittig.[83]

(i) *Reactions in the Gaseous Phase.*—Since the last Report on free radicals of short life [84] there have been no additions to the list of such radicals which have been proved to have a separate and independent existence. This is to be expected, since it is known that the higher alkyl radicals are very unstable and tend to break down into the simpler but more stable radicals. The main interest in this field of chemistry has now shifted from the preparation and detection of free radicals to physicochemical investigations connected with the elucidation of the actual rôle which these radicals play in reaction processes. Free radicals of short life, such as the lower alkyl radicals, are usually the initial products of either thermal or photochemical decompositions and much work has been carried out on the kinetics and reaction mechanisms of these processes. Such radicals are characterised by a high degree of reactivity and may react either with themselves or with molecules. In the latter case new radicals are formed and a chain reaction is initiated which may culminate either in the combination of two radicals to give a molecule or in disproportionation. The radicals are best detected by means of the Paneth technique of combination with a metallic deposit, but other methods of detection are available which depend on the use of radioactive indicators, the ortho-para hydrogen conversion, and exchange reactions. The study of the production and behaviour of free radicals in gaseous

[81] *J.*, 1939, 310; 1940, 880.   [82] *J.*, 1940, 874.
[83] *Angew. Chem.*, 1939, **52,** 89.   [84] *Ann. Reports*, 1937, **34,** 264.

reactions is one of wide importance in both pure and applied chemistry. The thermal decomposition or pyrolysis of hydrocarbons is a subject of great importance to the petroleum industry and it has been established for some time that such thermal reactions result primarily in the production of free alkyl radicals. The rôle of free radicals in elementary organic reactions has been discussed by F. O. Rice and E. Teller,[85] and the part played by free radicals in the mechanisms of gaseous explosions by A. R. Ubbelohde.[86] A detailed discussion of recent developments on the kinetics and reaction mechanisms of gaseous reactions involving free radicals does not fall within the scope of this Report, but an indication will be given in the following sections of some of the problems which are receiving attention.

Thermal decompositions. According to the free-radical theory of Rice,[87] the thermal decomposition of a pure organic compound occurs through the primary rupture of a carbon–carbon bond with the production of free radicals, followed by a chain reaction which is finally terminated either by a process of recombination or by a disproportionation reaction. Considerable attention has been paid to the thermal decomposition of hydrocarbons from this standpoint. A general study of the thermal decomposition of various petroleum hydrocarbons has been made by B. L. Evering,[88] who showed by means of reaction with lead mirrors that free radicals were formed. Analysis of the resulting lead alkyls gave the concentration of the various free radicals. The kinetics of the elementary reactions of the simpler hydrocarbons with particular reference to thermal decomposition and the free-radical theory have been reviewed by E. W. R. Steacie,[89] and F. O. Rice and O. L. Polly [90] have discussed the inhibition of homogeneous organic decompositions by means of nitric oxide.

Various aspects of the thermal decomposition of *n*-butane have been studied by E. W. R. Steacie and H. O. Folkins [91] and by F. O. Rice and O. L. Polly.[92] T. J. Gray and M. W. Travers [93] have studied the kinetics of the thermal decomposition of *neo-*

[85] *J. Chem. Physics*, 1938, **6,** 489; 1939, **7,** 199.

[86] *Chem. and Ind.*, 1940, **59,** 657.

[87] F. O. Rice and K. K. Rice, "The Aliphatic Free Radicals," Johns Hopkins Press, Baltimore, 1935.

[88] *J. Amer. Chem. Soc.*, 1939, **61,** 1400.

[89] *Chem. Reviews*, 1938, **22,** 311; cf. M. W. Travers, *J. Amer. Chem. Soc.*, 1939, **61,** 977.

[90] *J. Chem. Physics*, 1938, **6,** 273.

[91] *Canadian J. Res.*, 1939, **17,** *B,* 105; 1940, **18,** *B,* 1.

[92] *Trans. Faraday Soc.*, 1939, **35,** 850.

[93] *Ibid.*, p. 868.

pentane at 500—520° and R. Maess [94] has shown that free radicals, derived either from the thermal decomposition of azomethane or from the photolysis of azomethane or acetone, are capable of accelerating the thermal decomposition and oxidation of n-heptane. The thermal decomposition of octane has been investigated in detail by R. F. Marschner,[95] who showed that, although the results are in general similar to those predicted by the free-radical theory, certain important differences are to be found. He considers that it is not possible to predict with accuracy the products of the thermal decomposition of a paraffin as large as octane.

The reactions of methyl radicals with themselves and with hydrogen molecules have been discussed by H. A. Taylor and M. Burton.[96] Reactions of methyl radicals, derived from the photodecomposition of dimethylmercury, with deuterium, ethane, butane, isobutane, and neopentane,[97] and with benzene, toluene, diphenylmethane and propylene [98] have also been investigated. In the latter reactions methane is formed, $CH_3 + RH \longrightarrow CH_4$, and it is shown that the activation energy for the reaction with benzene is much higher than that for toluene, a result which provides a quantitative basis for the observations of F. Hein and H. J. Mesée [99] that, of the three possible scission products of the pyrolysis of toluene, Ph· + Me·, Me·C_6H_4· + H·, and Ph·CH_2· + H·, the last occurs almost exclusively, since with the Paneth mirror technique only dibenzylmercury was found in the products. F. O. Rice, W. D. Walters, and P. M. Ruoff [1] consider that it is unlikely that methyl radicals react with either ethers or primary amines to give an exchange reaction, thus :

$$Me + ROR' \longrightarrow ROMe + R'$$
$$Me + RNH_2 \longrightarrow MeNH_2 + R$$
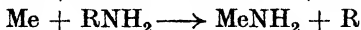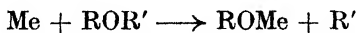
since both in the thermal decomposition of methyl ethyl ether and in its decomposition by the introduction of methyl radicals no dimethyl ether was to be found in the products. In similar manner no methylamine was to be found in the products of the decomposition of propylamine. The stability and mechanism of the decomposition of the ethyl, propyl, and acetyl radicals have been discussed by C. E. H. Bawn.[2]

The thermal decomposition of azomethane, both alone and in presence of nitric oxide, has been studied by H. A. Taylor and

[94] *Oel u. Kohle*, 1939, **15**, 299, 321.   [95] *Ind. Eng. Chem.*, 1938, **30**, 554.
[96] *J. Chem. Physics*, 1939, **7**, 675.
[97] J. O. Smith and H. S. Taylor, *ibid.*, p. 390.
[98] H. S. Taylor and J. O. Smith, *ibid.*, 1940, **8**, 543.
[99] *Naturwiss.*, 1938, **26**, 710.   [1] *J. Chem. Physics*, 1940, **8**, 259.
[2] *Trans. Faraday Soc.*, 1938, **34**, 598.

F. P. Jahn,[3] who postulate the intermediate formation of tetra-methylhydrazine

$$MeN{:}NMe \longrightarrow N_2 + 2Me{\cdot}$$
$$2Me{\cdot} + MeN{:}NMe \longrightarrow Me_2N{\cdot}NMe_2$$
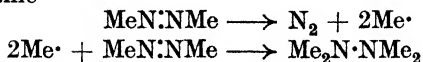
The formation of free alkyl radicals during the pyrolysis of acet-aldehyde at 500° has been demonstrated by M. Burton, J. E. Ricci, and T. W. Davis [4] by their ability to remove radio-lead mirrors. A free-radical mechanism has been suggested for the thermal decomposition of diacetyl.[5] The thermal decomposition of gaseous benzaldehyde has been investigated by R. E. Smith and C. N. Hinshelwood.[6] The main reaction may be represented thus : $Ph{\cdot}CHO \longrightarrow C_6H_6 + CO$, but the intermediate formation of the formyl radical is regarded as an essential stage in the process. Some p-substituted benzaldehydes have also been examined.[7]

Photochemical decompositions. A general discussion of the pro-duction and behaviour of alkyl radicals derived from photochemical processes has been published by H. S. Taylor,[8] which embraces the photolysis of alkyl iodides and metal alkyls as well as the mercury-sensitised decomposition of saturated hydrocarbons and hydro-genation of unsaturated hydrocarbons. The mercury-photosensi-tised reactions of ethane and propane have been studied by E. W. R. Steacie and his collaborators.[9] The reactions involved in the photolysis of aldehydes and ketones have been reviewed by P. A. Leighton [10] and special attention has been given to the mechanisms of the processes involved in the pyrolysis, the radical-induced decomposition, and the photodecomposition of acetaldehyde by M. Burton, H. A. Taylor, and T. W. Davis.[11] It is shown that the three processes are not identical, since in the photodecompos-ition and probably in the pyrolysis the formyl radical appears to be involved, whereas the acetyl radical seems to play a part in the radical-induced reaction.

W. J. Moore and H. S. Taylor [12] point out that a convenient method for the preparation of a free alkyl radical is by the addition

[3] *J. Chem. Physics*, 1939, **7**, 470, 474.

[4] *J. Amer. Chem. Soc.*, 1940, **62**, 265.

[5] F. O. Rice and W. D. Walters, *J. Chem. Physics*, 1939, **7**, 1015; W. D. Walters, *J. Amer. Chem. Soc.*, 1940, **62**, 880.

[6] *Proc. Roy. Soc.*, 1940, *A*, **175**, 131.

[7] R. E. Smith, *Trans. Faraday Soc.*, 1940, **36**, 983.

[8] *J. Physical Chem.*, 1938, **42**, 763.

[9] E. W. R. Steacie and N. W. F. Phillips, *J. Chem. Physics*, 1938, **6**, 179; *Canadian J. Res.*, 1938, *B*, **16**, 303; E. W. R. Steacie, W. A. Alexander, and N. W. F. Phillips, *ibid.*, p. 314; E. W. R. Steacie and D. J. Dewar, *J. Chem. Physics*, 1940, **8**, 571.

[10] *J. Physical Chem.*, 1938, **42**, 749.

[11] *J. Chem. Physics*, 1939, **7**, 1080.   [12] *Ibid.*, 1940, **8**, 504.

of a hydrogen atom to the olefin.   If the hydrogen atoms are produced by mercury photosensitisation, their concentration will be low compared with the radical concentration and subsequent reactions of the radicals with each other may then be studied.   It is shown that the mercury photosensitised hydrogenation of ethylene gives 84% of butane and 14% of ethane, whereas with propylene and n-butylene, which can give rise to both the n-alkyl radical and the *iso*alkyl radical by addition of a hydrogen atom, the products are 64% of hexane and 26% of propane, and 66% of octane and 29% of butane respectively, *i.e.*, there is a significantly greater formation of the hydrocarbon containing the same number of carbon atoms as the original olefin.

Among other topics which have received recent attention are the photolysis of zinc and mercury diethyls, which gives rise to the production of ethyl radicals,[13] the photolysis of acetaldehyde at high temperatures,[14] for which a mechanism almost identical with that put forward by F. O. Rice and K. F. Herzfeld [15] for the thermal decomposition of acetaldehyde is suggested, the photolysis of acetone,[16] and the photolysis of methyl ethyl ketone.[17]   H. H. Glazebrook and T. G. Pearson [18] show that the primary products of the photochemical decomposition of acetophenone react with tellurium to give diphenyl telluride, dimethyl telluride, and phenyl methyl telluride, whereas in the absence of tellurium the products are diphenyl, benzil, and probably 1 : 4-diphenylbutane-1 : 4-dione. These results clearly indicate the formation of methyl, phenyl, benzoyl, and probably benzoylmethyl radicals.   Similarly, in the photolysis of benzophenone, radicals are formed which remove a tellurium mirror and in the absence of tellurium yield diphenyl. These results on the phenyl radical are of particular interest, since F. A. Paneth and W. Lautsch [19] had previously concluded that the phenyl radical showed great instability and did not react with tellurium.

Work on the photodecomposition of azomethane has been continued by M. Burton, T. W. Davis, and H. A. Taylor,[20] T. W. Davis, F. P. Jahn, and M. Burton,[21] and by F. E. Blacet and A. Taurog.[22] C. H. Bamford [23] has examined the photolysis of aliphatic nitroso-amines and amines. In the case of dimethyl- and diethyl-nitroso-

[13] *Idem, J. Chem. Physics,* 1940, **8**, 396.
[14] D. C. Grahame and G. K. Rollefson, *ibid.*, p. 98.
[15] *J. Amer. Chem. Soc.*, 1934, **56**, 284.
[16] D. S. Herr and W. A. Noyes, jun., *ibid.*, 1940, **62**, 2052.
[17] W. J. Moore and H. S. Taylor, *J. Chem. Physics,* 1940, **8**, 466.
[18] *J.*, 1939, 589.   [19] *J.*, 1935, 380.
[20] *J. Amer. Chem. Soc.*, 1937, **59**, 1038, 1989.   [21] *Ibid.*, 1938, **60**, 10.
[22] *Ibid.*, 1939, **61**, 3024.   [23] *J.*, 1939, 12, 17.

amines the experimental results were interpreted by the formation of dialkylnitrogen radicals, *e.g.*,

$$(CH_3)_2N \cdot NO + h\nu \longrightarrow (CH_3)_2N \cdot + NO \quad . \quad . \quad . \quad . \quad . \quad (1)$$
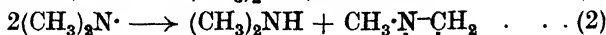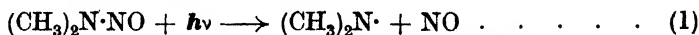
$$2(CH_3)_2N \cdot \longrightarrow (CH_3)_2NH + CH_3 \cdot N\text{--}CH_2 \quad . \quad . \quad . (2)$$
$$\downarrow$$
$$\text{polymer}$$

and the following mechanisms were indicated for the photodecompositions of primary, secondary, and tertiary amines :

$$(a) \quad R \cdot NH_2 + h\nu \longrightarrow R \cdot NH \cdot + H \cdot \quad . \quad . \quad . \quad . \quad (3)$$

$$2R \cdot NH \cdot \longrightarrow R \cdot NH_2 + R \cdot N \colon \quad . \quad . \quad . \quad . \quad (4)$$
$$\downarrow$$
$$\text{polymer}$$

$$2R' \cdot CH_2 \cdot NH \cdot \longrightarrow R' \cdot CH_2 \cdot N \colon CHR + NH_3 \cdot \quad . \quad (5)$$

$$(b) \quad RR'NH + h\nu \longrightarrow RR'N \cdot + H \cdot \quad . \quad . \quad . \quad . \quad (6)$$
Followed by reaction (2)
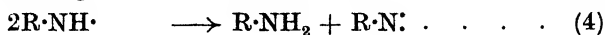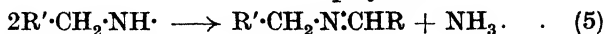
$$(c) \quad R_3N + h\nu \longrightarrow RRN \cdot + R \cdot \quad . \quad . \quad . \quad . \quad (7)$$
Followed by reaction (2)

Reactions between nitric oxide and nitrogen free radicals derived from the photolysis of ammonia and hydrazine have also been carried out by C. H. Bamford.[24] The nitric oxide reacts with the free radicals thus :

$$\cdot NH_2 + NO \longrightarrow N_2 + H_2O + 104 \text{ kg.-cals.}$$
$$\cdot NH \cdot NH_2 + NO \longrightarrow N_2O + NH_3 + 75 \text{ kg.-cals.}$$
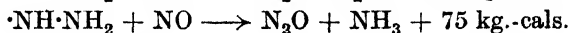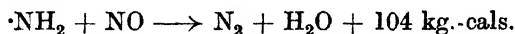
The primary dissociation of hydrazine into the $\cdot N_2H_3$ radical was confirmed by irradiation in the presence of propylene.

Atomic reactions. The reactions between sodium vapour and organic halides [25] have been shown to give rise to the formation of the sodium halide and an alkyl radical: $R \cdot Hal + Na \longrightarrow NaHal + R \cdot$. The evidence for radical formation ($R = Me$, Et, or Ph) in these reactions has in the past been based mainly on their behaviour with chlorine, iodine, or hydrogen,[26] but confirmatory evidence has now been provided by A. O. Allen and C. E. H. Bawn,[27] who employed the Paneth technique with antimony and tellurium mirrors. C. E. H. Bawn and R. F. Hunter [28] and C. E. H. Bawn and J. Milsted [29] have investigated the reactions between sodium

[24] *Trans. Faraday Soc.*, 1939, **35**, 568.
[25] M. Polanyi, " Atomic Reactions," Williams and Norgate, London, 1932.
[26] E. Horn, M. Polanyi, and D. W. G. Style, *Trans. Faraday Soc.*, 1934, **30**, 189; E. Horn and M. Polanyi, *Z. physikal. Chem.*, 1934, *B*, **25**, 151; H. von Hartel, *Trans. Faraday Soc.*, 1934, **30**, 187.
[27] *Trans. Faraday Soc.*, 1938, **34**, 463.
[28] *Ibid.*, p. 608.   [29] *Ibid.*, 1939, **35**, 889.

vapour and a series of aliphatic dibromides of the general formula $Br \cdot [CH_2]_n \cdot Br$, where $n = 1, 3, 4, 5$, or 6. These reactions are considered to give rise to the diradicals $[\cdot CH_2 \cdot]_n$, which show a minimum stability at $n = 4$. The bivalent methylene radical $(n = 1)$, which displays the nature of a very reactive molecule rather than that of a free radical, had been previously isolated by T. G. Pearson, R. H. Purcell, and G. S. Saigh [30] from both keten and diazomethane by thermal and photochemical methods, and its existence and participation in hydrocarbon reactions have been comprehensively reviewed by R. F. Barrow, T. G. Pearson, and R. H. Purcell.[31]

Gaseous nitration of paraffins. It has been suggested by R. F. McCleary and E. F. Degering [32] that the vapour-phase nitration of paraffinoid hydrocarbons proceeds by a mechanism involving free alkyl radicals. Oxidation or induced dissociation of the hydrocarbon results in the formation of the free alkyl radicals, which in turn react with nitric acid to give nitroparaffins. Methane is not susceptible to nitration in the gaseous phase, but with ethane, propane, *n*-butane, *iso*butane, *n*-pentane, and *iso*pentane the products isolated agree in every case with those to be expected from reaction with all the theoretically possible free radicals, which can be derived from the hydrocarbon either by loss of a hydrogen atom or by the fission of a carbon–carbon bond.[33] The results obtained in the vapour-phase nitration of the six paraffins and the free radicals obtainable in each case are tabulated on the next page.

The industrial application of the gaseous nitration of paraffin hydrocarbons is of considerable importance, since it provides a novel use for waste refinery gases and the products can find many valuable outlets in synthetic organic chemistry.

(ii) *Reactions in the Liquid Phase.*—The behaviour of free radicals of short life in solution will be fundamentally different from their behaviour in the gaseous phase. In the latter case the radical is present in a rarefied atmosphere in which collisions with like radicals and possibly with molecules of a very inert carrier gas can readily occur. On the other hand a radical of short life in solution will have little chance of colliding with a second radical and collisions with solvent molecules will predominate. In the case of two radicals derived in solution from one and the same molecule the Franck–Rabinowitsch principle of primary recombination may operate,[34]

[30] *J.*, 1938, 409. [31] *Trans. Faraday Soc.*, 1939, **35**, 880.
[32] *Ind. Eng. Chem.*, 1938, **30**, 64.
[33] H. B. Hass, E. B. Hodge, and B. M. Vanderbilt, *ibid.*, 1936, **28**, 339; H. B. Hass and J. A. Patterson, *ibid.*, 1938, **30**, 67; L. W. Seigle and H. B. Hass, *ibid.*, 1939, **31**, 648.
[34] J. Franck and E. Rabinowitsch, *Trans. Faraday Soc.*, 1934, **30**, 120.

Hydrocarbon.	Radicals.	Nitration products, %.	*	
Ethane	Methyl	Nitromethane	10—20	
	Ethyl	Nitroethane	80—90	
Propane	Methyl	Nitromethane	9	
	Ethyl	Nitroethane	26(?)	
	n-Propyl	1-Nitropropane	32	
	isoPropyl	2-Nitropropane	33	
n-Butane	Methyl	Nitromethane	6	
	Ethyl	Nitroethane	12	
	n-Propyl	1-Nitropropane	5	
	n-Butyl	1-Nitrobutane	27	
	sec.-n-Butyl	2-Nitrobutane	50	
isoButane	Methyl	Nitromethane	3	
	isoPropyl	2-Nitropropane	20	
	isoButyl	1-Nitroisobutane	65	
	tert.-Butyl	2-Nitroisobutane	7	
			†	
n-Pentane	Methyl	Nitromethane	1	
	Ethyl	Nitroethane	7	
	n-Propyl	1-Nitropropane	14	
	n-Butyl	1-Nitrobutane	12·5	
	n-Amyl	1-Nitropentane	22	
	a-Methyl-n-butyl	2-Nitropentane	21	
	a-Ethyl-n-propyl	3-Nitropentane	23	
			‡	*
isoPentane	Methyl	Nitromethane	6	2
	Ethyl	Nitroethane	6	6
	isoPropyl	2-Nitropropane	6	11
	sec.-n-Butyl	2-Nitrobutane }	12	10
	isoButyl	1-Nitroisobutane }		
	isoAmyl	1-Nitro-3-methylbutane	13	13
	β-Methyl-sec.-n-butyl	2-Nitro-3-methylbutane	27	16
	tert.-Amyl	2-Nitro-2-methylbutane	19	14
	β-Methyl-n-butyl	1-Nitro-2-methylbutane	11	28

* At 420°.   † At 400°.   ‡ At 380°.

i.e., the radicals are so constrained by a shell of solvent molecules that they cannot escape from each other and are caused to recombine. In most of the examples studied so far, reactions with solvent molecules are the rule rather than the exception and many instances could be cited in which faulty conclusions have been drawn in the past by failure to recognise the inherent distinction between the behaviour of such radicals in the gaseous phase and that of those in solution.

Alkyl radicals. The reactions of free alkyl radicals in solution have been investigated by C. H. Bamford and R. G. W. Norrish,[35] who studied the photolysis of a number of aliphatic aldehydes and ketones in solution in medicinal paraffin and in *iso*octane. As in the corresponding reactions in the gaseous phase, photolysis results

[35] J., 1938, 1531.

in reactions of two types, unimolecular elimination of carbon monoxide with formation of saturated hydrocarbons (Type I) :

$$R \cdot CHO \longrightarrow RH + CO$$
$$R \cdot COR' \longrightarrow (R_2 + RR' + R_2') + CO$$
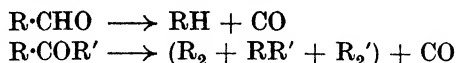
and formation of an olefinic hydrocarbon together with a simpler carbonyl compound (Type II) :

$$CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_2 {\overset{R}{\underset{}{>}}} CO \longrightarrow {\overset{R}{\underset{CH_3}{>}}} CO + CH_3 \cdot CH{:}CH_2$$
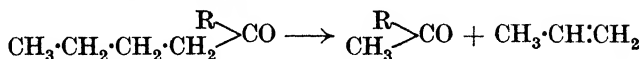
It is found, however, that, whereas reactions of type I in the case of aldehydes and of type II in the case of both aldehydes and ketones remain unmodified by any secondary reactions in solution, reactions of type I in the case of ketones suffer a profound modification, since the free alkyl radicals R and R' react with the solvent (at 70—100°) and become hydrogenated with the production of equivalent unsaturation in the solvent. This sequence of reactions may be represented as follows :

$$CH_3 \cdot CO \cdot C_2H_5 \longrightarrow C_2H_5 \cdot + CH_3 \cdot CO \cdot$$
$$CH_3 \cdot CO \cdot \longrightarrow CH_3 \cdot + CO$$
$$CH_3 \cdot + RH \longrightarrow CH_4 + R \cdot$$
$$C_2H_5 \cdot + RH \longrightarrow C_2H_6 + R \cdot$$
$$CH_3 \cdot CO \cdot + RH \longrightarrow CH_3 \cdot CHO + R \cdot$$
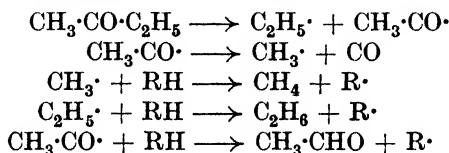
where RH represents a saturated aliphatic hydrocarbon. The large paraffinoid radicals R· can then undergo disproportionation to give an olefinic and a saturated molecule :

$$C_nH_{2n+1} + C_nH_{2n+1} \longrightarrow C_nH_{2n} + C_nH_{2n+2}$$
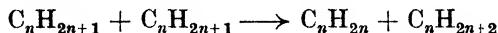
At room temperature the photolysis of ketones in solution by means of a reaction of type I is entirely suppressed owing to the operation of the Franck–Rabinowitsch principle of primary recombination.[36] The secondary reaction of the free radicals with the solvent is thus profoundly affected by temperature. This temperature dependence and also the development of unsaturation in the hydrocarbon solvent constitute a valuable qualitative test for the presence of free radicals in solution. The reaction of free radicals with aliphatic hydrocarbon solvents, resulting in the abstraction of hydrogen from them, has previously been shown to be characteristic of aryl radicals in solution.[37]

P. L. Cramer [38] has shown that ethyl radicals, prepared *in situ* by thermal decomposition of lead tetraethyl, react with liquid

[36] Compare C. H. Bamford and R. G. W. Norrish, *J.*, 1938, 1544.
[37] D. H. Hey and W. A. Waters, *Chem. Reviews*, 1937, **21**, 169.
[38] *J. Amer. Chem. Soc.*, 1938, **60**, 1406.

aliphatic and hydroaromatic hydrocarbons.   With saturated hydrocarbons hydrogenation takes place with formation of a new radical :
$Et\cdot + RH \longrightarrow C_2H_6 + R\cdot$; with unsaturated hydrocarbons an addition reaction takes place, giving a new saturated radical :
$Et\cdot + R\cdot CH:CH_2 \longrightarrow R\cdot CHEt\cdot CH_2\cdot$.   On the other hand ethyl radicals are stated to have no effect on liquid benzene or naphthalene under the conditions here employed.

Aryl radicals.   The evidence for the production of free aryl radicals in reactions of the diazo-hydroxides, nitrosoacylarylamines, arylazotriarylmethanes, and diaroyl peroxides in solution has been reviewed in a previous Report.[39]   In brief, the main evidence depends on (*a*) reaction between the radicals and aromatic compounds to give substitution products, such reactions not obeying the laws of aromatic substitution, (*b*) reaction between the radicals and aliphatic hydrogen- and halogen-containing solvents, resulting in an abstraction of hydrogen and halogen respectively, thus, $Ar\cdot + RH \longrightarrow ArH$ and $Ar\cdot + RHal \longrightarrow ArHal$, and (*c*) liberation of carbon dioxide and attack on inert metals in the reactions of the nitrosoacylarylamines.   One of the most remarkable features arising out of the collected evidence is the qualitative differentiation which is revealed between aliphatic-bound hydrogen and aromatic-bound hydrogen.   In the former case the radical abstracts hydrogen,

$$R\cdot + R'H \longrightarrow RH + R'\cdot$$
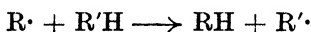
whereas in the latter case the radical displaces hydrogen,

$$R\cdot + R''H \longrightarrow RR'' + H\cdot$$
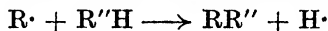
There is, however, no sharp division between these two types and cases have been recorded in which both reactions occur at the same time.

Much confirmatory evidence has now come to light in support of the existence and participation of free aryl radicals in many reactions in solution.   W. A. Waters has made a comprehensive study of the reactions of benzenediazonium chloride under organic solvents.[40]   It is concluded that the primary reaction is the decomposition of a wholly covalent molecule, diazobenzene chloride, into a free phenyl radical, a chlorine atom and nitrogen :

$$Ph\cdot N:NCl \longrightarrow Ph\cdot + N_2 + Cl\cdot$$
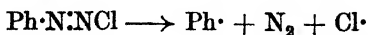
When suspended in acetone, hexane, or carbon tetrachloride, benzenediazonium chloride decomposes with liberation of hydrogen chloride and formation of some chlorobenzene.   If the reaction

[39] *Ann. Reports,* 1937, **34**, 282.   [40] *J.,* 1937, 2007.

with acetone is carried out in presence of an excess of calcium carbonate, it gives mainly benzene and chloroacetone :

$$Ph\cdot + CH_3\cdot CO\cdot CH_3 \longrightarrow PhH + CH_3\cdot CO\cdot CH_2\cdot$$
$$Cl\cdot + CH_3\cdot CO\cdot CH_3 \longrightarrow Cl\cdot CH_2\cdot CO\cdot CH_3 + H\cdot$$
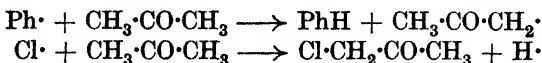
and under these conditions metals such as antimony, bismuth, lead, tin, nickel, iron, copper, silver, and mercury are all attacked. In most of these cases the metallic chlorides are formed, but with mercury the product contains phenylmercuric chloride and with antimony some triphenylstibine dichloride is formed. Similar reactions were also carried out with a number of substituted benzenediazonium chlorides [41] and an extensive survey was later reported on the behaviour of a large variety of metallic elements in this reaction.[42] In many cases the metal halides are formed, but in others true organometallic compounds are isolated. The reaction in presence of antimony, under either acetone or ethyl acetate, has been developed into a new preparative method for aromatic antimonials [43] and a corresponding reaction with arsenic provided a new route to aromatic arsenicals.[44] Reactions have also been carried out between benzenediazonium chloride and sulphur, selenium and tellurium under acetone and in presence of calcium carbonate.[45] In each case the element was attacked, giving diphenyl sulphide, diphenyl selenide, and diphenyltellurium dichloride respectively. No reaction appeared to take place with red phosphorus, boron, or silicon.

Further reactions of the diazohydroxides have also been investigated by W. A. Waters,[46] which support the view that its decomposition gives rise to free phenyl and hydroxyl radicals. Decomposition of diazobenzene hydroxide, $Ph\cdot N\colon N\cdot OH$, in carbon disulphide gives diphenyl disulphide, and decomposition in *cyclo*-hexane gives benzene. The almost universal reaction of diazobenzene hydroxide with a solvent of any type renders extremely difficult the application of the Gomberg reaction to solid reactants in solution.[47] Limited success was obtained with the use of carbon tetrachloride or chloroform, but even here chlorobenzene was formed in appreciable yield. The known oxidising reactions of diazobenzene hydroxide are also shown to be in agreement with the fission of the diazo-hydroxide into radicals. It may be noted

[41] F. B. Makin and W. A. Waters, *J.*, 1938, 843.

[42] W. A. Waters, *J.*, 1939, 864.   [43] *Loc. cit.* (ref. 41).

[44] W. A. Waters, *Nature*, 1938, 142, 1077.

[45] *Idem, J.*, 1938, 1077.

[46] *J.*, 1937, 2014.

[47] W. S. M. Grieve and D. H. Hey, *J.*, 1938, 108; I. M. Heilbron, D. H. Hey, and R. Wilkinson, *ibid.*, p. 699.

that O. Neunhoeffer and J. Weise [48] have shown that diazonium compounds couple with 2-hydroxy-1 : 4-naphthaquinone in presence of acetic acid in the normal manner, a reaction obviously involving diazonium cations, whereas in presence of alkali nitrogen is evolved and a 2-hydroxy-3-aryl-1 : 4-naphthaquinone results from the fission of the diazo-hydroxide into free radicals.

W. E. Hanby and W. A. Waters [49] have investigated the reactions of various benzenediazonium chlorides under esters and nitriles. These reactions result in some replacement of the $-N_2Cl$ group by either hydrogen or chlorine, and, as with the reactions under acetone, metallic elements added to the reaction mixture are attacked.   In the reactions with nitriles indications were obtained of an addition process, involving free radicals, by the isolation of an acetarylamide, the formation of which may be represented thus :

$$Ar\cdot + Cl\cdot + CH_3\cdot CN \longrightarrow CH_3\cdot CCl\colon NAr$$
$$CH_3\cdot CCl\colon NAr + H_2O \longrightarrow CH_3\cdot CO\cdot NHAr + HCl$$
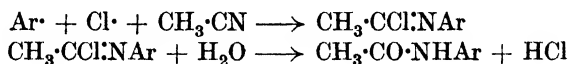
Similar addition reactions have been observed by H. Meerwein, E. Büchner, and K. van Emster,[50] who have shown that aromatic diazonium chlorides, in presence of sodium acetate and acetone or pyridine, add on to $\alpha\beta$-unsaturated compounds such as methyl cinnamate and methyl fumarate.   When acetone is used, it becomes converted into chloroacetone, as observed by W. A. Waters.   These reactions may be regarded as involving free aryl radicals and chlorine atoms, which thus show additive properties towards unsaturated organic molecules as well as towards metals.   The sodium acetate may serve to convert the diazonium chloride into the corresponding acetate (I), which can pass readily into the covalent acetyl derivative of the diazo-hydroxide (II), which is probably the active agent responsible for the production of the free radicals in these reactions as well in those of the nitroso-acylarylamines (III) :

$$Ar\cdot N\colon N\}Cl + CH_3\cdot CO_2Na \rightleftharpoons Ar\cdot N\colon N\}\cdot O\cdot CO\cdot CH_3 + NaCl$$
$$\big\Updownarrow \text{ (I.)}$$

(III.) $Ar\cdot N(NO)\cdot CO\cdot CH_3 \rightleftharpoons Ar\cdot N\colon N\cdot O\cdot CO\cdot CH_3$ (II.)
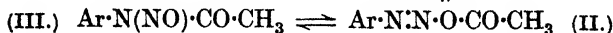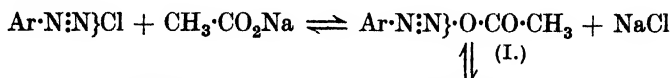
On the other hand it has been shown by W. A. Waters [51] that, when nitrosoacetanilide reacts with *cyclo*hexene in presence of calcium carbonate, some Δ^2-*cyclo*hexenyl acetate is formed, and when the nitrosoacetanilide is replaced by benzenediazonium chloride in suspension in acetone, some Δ^2-*cyclo*hexenyl chloride

48 *Ber.*, 1938, **71**, 2703.   49 *J.*, 1939, 1792.
50 *J. pr. Chem.*, 1939, [ii], **152**, 237.   51 *J.*, 1939, 1805.

results. These reactions are regarded as substitution reactions at the reactive methylene group in the *cyclo*hexene molecule by the acetate radical and chlorine atom respectively, or alternatively as addition reactions, involving two acetate radicals and two chlorine atoms respectively, followed by an elimination reaction to give the same products. Similar results have previously been recorded for the oxidation of *cyclo*hexene by lead tetra-acetate and by oxygen in presence of osmium and it is suggested that the above oxidation processes have in common a reaction mechanism which involves an attack on the *cyclo*hexene molecule by neutral radicals formed from the oxidising agent.

A study of the reactions of the reactive *syn*-diazo-cyanides in absence of water [52] provides additional evidence for the formation of free radicals and their reactions with solvent molecules. With carbon tetrachloride, benzene, and ether as solvents the products derived from the *syn*-diazobenzene cyanide, $Ar \cdot N \colon N \cdot CN$, in presence of copper-powder are a chlorobenzene $ArCl$, a diphenyl derivative $ArPh$, and a hydrocarbon derivative ArH respectively, thus simulating the behaviour of the diazoacetates (nitrosoacetanilides), the diazo-hydroxides and the diazo-chlorides, all of which involve the decomposition of a covalent molecule and not a diazonium kation. Under the experimental conditions here employed, the formation of the aromatic nitrile is suppressed. This reaction (the Gattermann reaction), which is also catalysed by copper, $Ar \cdot N_2 \cdot CN \xrightarrow{Cu} Ar \cdot CN + N_2$, is favoured only when ionisation is possible and is probably a reaction of the diazonium salt.

It has previously been shown [53] that, in agreement with the hypothesis that the primary reaction of nitrosoacetanilide with an aromatic solvent is its decomposition into phenyl and acetate radicals together with nitrogen, the rates of decomposition of nitrosoacetanilide as measured by the nitrogen evolved were independent, or nearly so, of the aromatic solvent. The reactions were unimolecular in type and the velocity constants were all of the same order. Similar measurements have now been described with a variety of non-aromatic solvents [54] and it is again shown that the velocity constants are not appreciably affected by the nature of the solvent. The free radicals resulting from the primary reaction invariably react with the solvent.

An extensive investigation of the reactions of nitrosoacylarylamines of various types has been described by J. W. Haworth and D. H. Hey,[55] which provides much further evidence for their

[52] O. Stephenson and W. A. Waters, *J.*, 1939, 1796.
[53] W. S. M. Grieve and D. H. Hey, *J.*, 1934, 1797.
[54] E. C. Butterworth and D. H. Hey, *J.*, 1938, 116.   [55] *J.*, 1940, 361.

primary decomposition into free radicals. It has been shown that a nitrosoacylarylamine may react with a hydrocarbon RH in one of two ways :

(A) $Ar \cdot N(NO) \cdot CO \cdot CH_3 + RH \longrightarrow ArR + N_2 + CH_3 \cdot CO_2H$

(B) $Ar \cdot N(NO) \cdot CO \cdot CH_3 + RH \longrightarrow ArH + N_2 + (CH_3 \cdot CO_2R)$
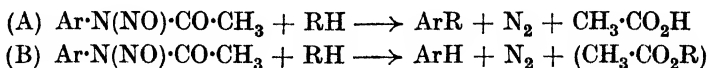
Reaction (A) predominates when R = aryl, whereas reaction (B) is predominant when R = alphyl.[56] This dual reactivity is found also with certain reactions of the diaroyl peroxides and of the diazo-compounds.[57] The reactions of various nitrosoacetanilides with aromatic solvents have been widely extended, mainly for preparative purposes, and this work provides many more examples of the characteristic non-adherence to the laws of aromatic substitution which is to be expected from a reaction mechanism involving the participation of free radicals.[58] In most cases ortho-para substitution is the general rule, but in the reactions between 4-nitroso-acetamidodiphenyl and both chloro- and bromo-benzene it was found that substitution by the diphenylyl group took place at all three positions in the halogenobenzene nucleus, giving the 2-, 3-, and 4-halogeno-p-terphenyls, which agrees with a previous observation that the reaction between diazobenzene hydroxide and ethyl benzoate gave 2-, 3-, and 4-diphenylcarboxylic esters.[59] The concomitant formation of all three isomerides in these reactions is in agreement with their representation as non-ionic processes involving the participation of neutral free radicals as opposed to the normal polar mechanism of aromatic substitution by kationoid and anionoid reagents.

Reactions have been carried out between both aromatic diazonium chlorides and nitrosoacylarylamines and pyridine.[60] In both cases mixtures of α-, β-, and γ-arylpyridines are formed, frequently in good yield. The formation of all three isomerides again points to a non-ionic mechanism, since an ionic mechanism would be expected to give an arylpyridinium chloride, or, by a subsequent migration, the α- and γ-isomerides only. It is probable that an addition

[56] Compare I. M. Heilbron, D. H. Hey, and A. Lambert, *J.*, 1940, 1279.

[57] H. Gelissen and P. H. Hermans, *Ber.*, 1925, **58**, 984.

[58] I. M. Heilbron, D. H. Hey, and R. Wilkinson, *J.*, 1938, 113; H. France, I. M. Heilbron, and D. H. Hey, *J.*, 1938, 1364; 1939, 1283, 1288; E. C. Butterworth, I. M. Heilbron, D. H. Hey, and R. Wilkinson, *J.*, 1938, 1386; D. H. Hey and S. E. Lawton, *J.*, 1940, 374.

[59] D. H. Hey, *J.*, 1934, 1967.

[60] J. W. Haworth, I. M. Heilbron, and D. H. Hey, *J.*, 1940, 349, 358, 372; E. C. Butterworth, I. M. Heilbron, and D. H. Hey, *ibid.*, p. 355; I. M. Heilbron, D. H. Hey, and A. Lambert, *ibid.*, p. 1279.

compound is first formed such as (IV) or (V), which subsequently decomposes into radicals which react with free pyridine, but it is

(IV.) $Ar \cdot N \vdots N \cdot N \underset{\underset{Cl}{\smile}}{\diagup} \bigcirc$ $Ar \cdot N \vdots N \cdot N \diagdown \bigcirc \diagdown \overset{Cl}{\underset{H}{<}}$ (V.)

also possible that, as in the Gomberg reaction, the active agent may again be the diazo-hydroxide produced thus :

$$C_5H_5N + Ar \cdot N_2Cl + H_2O \rightleftharpoons C_5H_5N,HCl + Ar \cdot N \vdots N \cdot OH$$
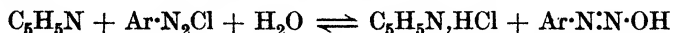
This reaction with pyridine bears some resemblance to the decomposition of mixed aliphatic-aromatic triazenes of the type $Ph \cdot N \vdots N \cdot NMe_2$ in boiling benzene solution in presence of hydrogen chloride, giving diphenyl, nitrogen, and dimethylamine hydrochloride : [61]

$$Ph \cdot N \vdots N \cdot NMe_2 + C_6H_6 + HCl \longrightarrow Ph_2 + N_2 + NHMe_2,HCl$$
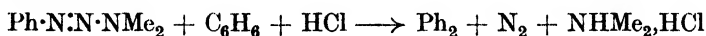
It may be recalled that reactions between diazobenzene hydroxide,[62] benzeneazotriphenylmethane,[63] and dibenzoyl peroxide [64] and pyridine have already been described. These reactions are said to give rise to a mixture of α- and γ-phenylpyridine, but it is more than probable that a closer examination of the products would reveal the presence of the β-isomeride also. This has already been achieved in the case of the reaction with dibenzoyl peroxide.[65]

Further light has been thrown on the chemistry of the reactions of the diacyl peroxides by H. Wieland, T. Ploetz, and H. Indest.[66] Of particular interest is the action of dibenzoyl peroxide on triphenylmethyl in benzene solution, which gave, with other products, tetraphenylmethane, but it is shown that the fourth phenyl group is not derived from the dibenzoyl peroxide, since tetraphenylmethane was also formed when di-p-phenylbenzoyl peroxide replaced the dibenzoyl peroxide. The following reactions were suggested, which indicate that the fourth phenyl group is supplied by the benzene :

$$Ph \cdot CO \cdot O \cdot O \cdot CO \cdot Ph + Ph_3C \cdot \longrightarrow Ph \cdot CO \cdot O \cdot CPh_3 + Ph \cdot CO \cdot O \cdot$$
$$Ph \cdot CO \cdot O \cdot + C_6H_6 \longrightarrow Ph \cdot CO_2H + Ph \cdot$$
$$Ph \cdot + Ph_3C \cdot \longrightarrow CPh_4$$
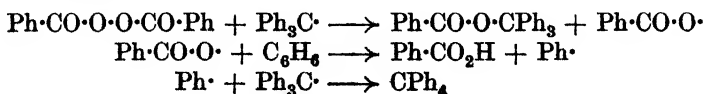
F. Fichter and H. Stenzl [67] have investigated the application of the Kolbe electrosynthesis to various aromatic acids in pyridine

[61] I.G., B.P. 513,846.
[62] M. Gomberg and W. E. Bachmann, *J. Amer. Chem. Soc.*, 1924, **46**, 2339.
[63] H. Wieland *et al.*, *Annalen*, 1934, **514**, 155.
[64] J. Overhoff and G. Tilman, *Rec. Trav. chim.*, 1929, **48**, 993.
[65] D. H. Hey and E. W. Walker, unpublished result.
[66] *Annalen*, 1937, **532**, 166.   [67] *Helv. Chim. Acta*, 1939, **22**, 970.

solution, which eliminates the complications arising from the presence of anodic oxygen. From benzoic acid, some γ-phenyl-pyridine (and possibly some α-phenylpyridine) and diphenyl-4-carboxylic acid are formed in addition to diphenyl. Similar products are formed during the thermal decomposition of dibenzoyl peroxide in pyridine solution, which indicates that the peroxide is formed as an intermediate product at the anode during electrolysis. Such an inference is not justified, since both the phenylpyridines and the diphenylcarboxylic acid are the normal products to be expected from the reactions of the free radicals which would be produced on discharge of the ions at the electrodes.[68]   The reactions may be represented as follows :

$$Ph\cdot CO_2H \longrightarrow Ph\cdot CO\cdot O^- + H^+$$
$$Ph\cdot CO\cdot O^- - e \longrightarrow Ph\cdot CO\cdot O\cdot$$
$$Ph\cdot CO\cdot O\cdot \longrightarrow Ph\cdot + CO_2$$
$$Ph\cdot + C_5H_5N \longrightarrow Ph\cdot C_5H_4N + H\cdot$$
$$Ph\cdot + Ph\cdot CO_2H \longrightarrow Ph\cdot C_6H_4\cdot CO_2H + H\cdot$$
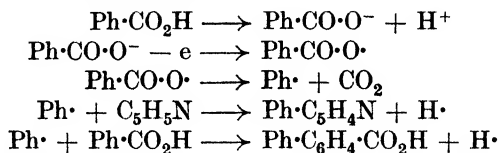
W. J. Hickinbottom [69] has shown that free radicals are formed in the Claisen rearrangement of phenyl benzyl ether to the corresponding o-substituted phenol which takes place on heating.   When this ether is heated in quinoline solution, benzyl- and phenoxy-quinolines together with toluene may be formed at the expense of the benzyl-phenol, and, since both the benzyl and the phenoxyl group attack the same position in the quinoline nucleus, a primary scission into benzyl and phenoxyl radicals is indicated.   The sequence of reactions may be represented thus :

$$Ph\cdot O\cdot CH_2Ph \longrightarrow Ph\cdot O\cdot + Ph\cdot CH_2\cdot$$
$$Ph\cdot CH_2\cdot + C_9H_7N \longrightarrow Ph\cdot CH_2(C_9H_6N) + H\cdot$$
$$Ph\cdot O\cdot + C_9H_7N \longrightarrow PhO\cdot(C_9H_6N) + H\cdot$$
$$Ph\cdot CH_2\cdot + H\cdot \longrightarrow Ph\cdot CH_3$$
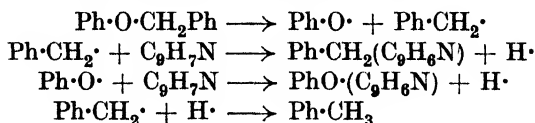
Such reactions with quinoline bear a close resemblance to the reactions between nitrosoacetanilide and pyridine cited above. Preliminary work on the action of nitrosoacetanilides on quinoline gives similar results.[70]   Evidence for the participation of free radicals in the rearrangement of phenyl alkyl ethers has also been contributed by O. Mumm, H. Hornhardt, and J. Diederichsen.[71] The various aspects of rearrangements of this type have been recently reviewed.[72]

[68] Compare also O. J. Walker and G. L. E. Wild, *J.*, 1937, 1132; H. Erlenmeyer and W. Schoenauer, *Helv. Chim. Acta*, 1937, **20**, 222, 1015.
   [69] *Nature*, 1938, **142**, 830; 1939, **143**, 520.
   [70] D. H. Hey, unpublished work.   [71] *Ber.*, 1939, **72**, 100.
   [72] *Ann. Reports*, 1939, **36**, 205.

M. S. Kharasch, W. Goldberg, and F. R. Mayo [73] have made some interesting observations on the catalytic reaction of Grignard reagents with hydrocarbons, which is attributed to the participation of free radicals. Addition of water during the preparation of the Grignard reagent from bromobenzene gives rise to diphenyl, yet it is known that phenylmagnesium bromide itself does not react with bromobenzene to give diphenyl. It is now shown that in the presence of traces of water, magnesium and a minimum of ether the Grignard reagent reacts with aromatic hydrocarbons, but not with hydroaromatic hydrocarbons. Thus benzylmagnesium chloride reacts with benzene to give diphenylmethane, with m-xylene to give 2 : 4-dimethyldiphenylmethane, and with mesitylene to give 2 : 4 : 6-trimethyldiphenylmethane, and in similar manner phenylmagnesium bromide reacts with toluene, m-xylene, mesitylene and chlorobenzene to give a methyl-, dimethyl-, trimethyl-, and chloro-diphenyl respectively. In each case a simultaneous reaction gives some diphenylethane from the benzyl compound and some diphenyl from the phenyl compound. Neither benzylmagnesium chloride nor phenylmagnesium bromide reacts with *cyclo*hexane. The properties attributed to the benzyl and phenyl radicals in these substitution reactions with aromatic compounds, together with the complete absence of such a reaction with *cyclo*hexane, are in agreement with the behaviour of phenyl radicals derived from other sources.[74] The participation of free radicals in the preparation and in certain reactions of Grignard reagents is indicated in many other observations.[75]

Free phenyl radicals are formed when organo-metallic compounds such as diphenylmercury, tetraphenyltin, and tetraphenyl-lead are heated and decomposition reactions with such compounds have been carried out in presence of solvents.[76] For example, phenyl radicals derived from diphenylmercury react with alcohols to give benzene, an aldehyde and an ester, thus :

$$HgPh_2 \longrightarrow Hg + 2Ph\cdot$$
$$2Ph\cdot + R\cdot CH_2\cdot OH \longrightarrow R\cdot CHO + 2C_6H_6$$
$$2R\cdot CHO \longrightarrow R\cdot CO_2\cdot CH_2R$$
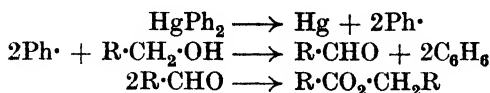
It must be conceded that there is now available a mass of evidence, derived from many sources, which is consistent within itself and

[73] *J. Amer. Chem. Soc.*, 1938, **60,** 2004.

[74] See D. H. Hey and W. A. Waters, *Chem. Reviews*, 1937, **21,** 169.

[75] See W. E. Bachmann, Ch. V, " Organic Chemistry," Ed. by H. Gilman, John Wiley and Sons, Inc., New York, 1938.

[76] G. A. Razuvaiev and M. M. Koton, *J. Gen. Chem., Russia*, 1931, **1,** 864; 1935, **5,** 361; M. M. Koton, *ibid.*, 1938, **8,** 1791; 1939, **9,** 1622, etc.

gives a convincing indication of the participation of free aryl radicals in a wide variety of reactions in solution.

The Wurtz and the Fittig reaction. The mechanism of these two reactions continues to attract attention. Mechanisms involving the formation of free radicals, as in the related vapour-phase atomic reactions of Polanyi, have been put forward, *e.g.*,

$$C_2H_5I + Na \longrightarrow NaI + C_2H_5\cdot$$
$$2C_2H_5\cdot \longrightarrow C_4H_{10}$$
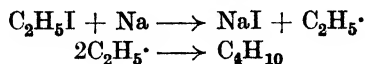
and equally convincing evidence indicates the intermediate formation of an organometallic compound, *e.g.*,

$$C_2H_5I + 2Na \longrightarrow C_2H_5Na + NaI$$
$$C_2H_5Na + C_2H_5I \longrightarrow C_4H_{10} + NaI$$
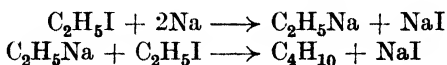
There can be no doubt that in many cases such organometallic derivatives are formed as intermediates in these reactions, but this does not necessarily exclude the intermediate formation of free radicals as well.[77] The formation of both ethylene and ethane as by-products in the reaction between ethyl iodide and sodium provides strong evidence for the participation of ethyl radicals.[78] The mechanism of the reaction between sodium and ethyl iodide in boiling hexane solution has recently been studied by R. B. Richards [79] from the kinetic standpoint. It is shown that the results are consistent with the free-radical theory and the main stages involved in the reaction are represented as follows :

$$C_2H_5I + Na \text{ (surface)} \longrightarrow C_2H_5\cdot + NaI$$
$$2C_2H_5\cdot \longrightarrow C_2H_4 + C_2H_6$$
$$C_2H_5\cdot + C_2H_5I \longrightarrow C_4H_{10} + I\cdot$$
$$I\cdot + Na \text{ (surface)} \longrightarrow NaI$$
$$C_2H_5\cdot + C_6H_{14} \longrightarrow C_2H_6 + C_6H_{13}\cdot$$
$$C_2H_5\cdot + C_6H_{13}\cdot \longrightarrow C_8H_{18}$$
$$C_2H_5\cdot + C_2H_4 \longrightarrow C_4H_9\cdot$$
$$C_4H_9\cdot + C_2H_4 \longrightarrow C_6H_{13}\cdot, \text{ etc.}$$
$$C_{n+2}H_{2n+5} \longrightarrow C_nH_{2n} + C_2H_5\cdot$$
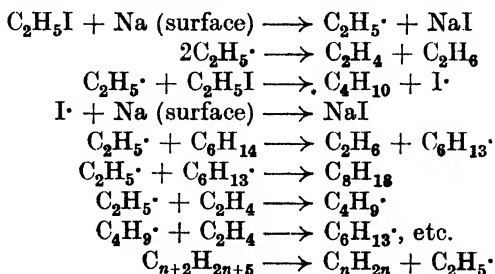
Such a scheme is in agreement with the results reported by A. A. Morton and G. M. Richardson [80] on the action of sodium on amyl chloride. It is shown that on adding amyl chloride to varying

[77] Compare A. A. Morton and I. Hechenbleikner, *J. Amer. Chem. Soc.*, 1936, **58**, 2599.

[78] W. Hückel, A. Kraemer, and F. Thiele, *J. pr. Chem.*, 1935, [ii], **142**, 207.

[79] *Trans. Faraday Soc.*, 1940, **36**, 956.

[80] *J. Amer. Chem. Soc.*, 1940, **62**, 123.

excesses of sodium, the yield of decane falls as the sodium/amyl chloride ratio is increased. With the larger excesses of sodium the chloride would be rapidly removed and the initially formed amyl radicals would undergo disproportionation or react with sodium rather than with amyl chloride to form decane.

In the reaction of sodium with chlorobenzene the products are benzene, diphenyl, p-terphenyl, o-terphenyl, 2 : 2'-diphenyldiphenyl and triphenylene. The formation of these compounds has been attributed by W. E. Bachmann and H. T. Clarke [81] to the intermediate formation of phenyl radicals, which can undergo both association and disproportionation. Although the formation of triphenylene may best be explained as a result of disproportionation, which gives the phenylene diradical, thus,

$$2C_6H_5\cdot \longrightarrow C_6H_6 + C_6H_4\cdot\cdot$$
$$3C_6H_4\cdot\cdot \longrightarrow C_6H_4 \underset{C_6H_4}{\overset{C_6H_4}{<}}$$
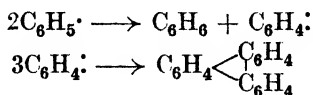
such a reaction is not necessary to explain the formation of the other polycyclic hydrocarbons, which can arise from the direct action between the phenyl radical and a hydrocarbon molecule. The probability of a reaction of this type is indicated by the fact that, if the reaction is carried out in presence of an excess of toluene, diphenyl is not formed but instead 4-methyldiphenyl and diphenylmethane are produced. A. A. Morton, J. T. Massengale, and G. M. Richardson [82] have correctly pointed out that it is not a characteristic property of phenyl radicals to dimerise in solution, but this does not exclude the possibility of the participation of free radicals in the formation of the polycyclic hydrocarbons and the presence of benzene may result either from the disproportionation reaction or more probably from the direct action of the phenyl radical with any hydrogen-containing molecule. O. Blum-Bergmann [83] has shown that the action of sodium on bromobenzene in presence of benzene gives mainly diphenyl together with some o-terphenyl and triphenylene and suggests that free phenyl radicals are involved, which undergo disproportionation. A more probable explanation is that reaction ensues between the phenyl radicals and benzene to give diphenyl, and between phenyl radicals and diphenyl to give o-terphenyl. The suggestion is also made that in the decomposition of benzeneazotriphenylmethane [84] the occurrence of benzene instead of the phenyl radical may be due to dispro-

[81] J. Amer. Chem. Soc., 1927, 49, 2089.
[82] Ibid., 1940, 62, 126.   [83] Ibid., 1938, 60, 1999.
[84] H. Wieland, E. Popper, and H. Seefried, Ber., 1922, 55, 1816.

portionation with the incidental formation of triphenylene.   There
is no evidence to support this view of the formation of benzene in
this reaction, which may more correctly be attributed to the well-
founded characteristic of the phenyl radical of abstracting hydrogen
from other molecules.

Atomic chlorination and bromination.   A number of reactions
which show a characteristic departure from the laws of aliphatic
substitution have recently been reported by M. S. Kharasch and
his co-workers.   These may be regarded as a counterpart of the
abnormal aromatic substitution reactions previously attributed to
aryl radicals.   In the aliphatic series the substituting agent is the
chlorine atom or the SO_2Cl radical.   M. S. Kharasch and H. C.
Brown [85] have shown that in presence of benzoyl peroxide abnormal
chlorination of fatty acids and acyl chlorides can be effected in the
dark with sulphuryl chloride.   Sulphuryl chloride normally furnishes
chlorine molecules, but in presence of a peroxide it can be used as a
source of chlorine atoms.[86]   Such chlorination takes place mainly
at the β- and γ-positions in the alkyl chain of the acid and similar
results have been reported for the photo-chlorination of fatty acids.
A chain reaction involving chlorine atoms is thus indicated.   More
recently H. C. Brown, M. S. Kharasch, and T. H. Chao [86a] have
shown that both the peroxide-catalysed and the photochemical
chlorination of primary active amyl chloride (+ 1-chloro-2-methyl-
butane) give rise to inactive 1 : 2-dichloro-2-methylbutane, which
indicates that these reactions proceed through a mechanism
involving the transient existence of a free radical (RH + Cl· ⟶
R· + HCl) rather than one involving the expulsion of a hydrogen
atom and a Walden inversion (RH + Cl· ⟶ RCl + H·).   It has
also been shown that the side-chain bromination of toluene is
favoured by conditions which give rise to atomic bromine, whereas
the nuclear substitution is a slow bimolecular reaction.[87]   In
presence of light, sulphuryl chloride can act as a sulphonating
agent for aliphatic hydrocarbons and acids through the agency
of the SO_2Cl radical.[88]   In the case of the hydrocarbons a catalyst
such as pyridine is required, but with the aliphatic acids no such
catalyst is necessary.   The acids are sulphonated at the β- and
γ-carbon atoms and never at the α-carbon atom.   The suggested

[85] *J. Amer. Chem. Soc.*, 1940, **62**, 925.

[86] *Idem, ibid.*, 1939, **61**, 2142.

[86a] *Ibid.*, 1940, **62**, 3435.

[87] M. S. Kharasch, E. Margolis, P. C. White, and F. R. Mayo, *ibid.*,
1937, **59**, 1405; M. S. Kharasch, P. C. White, and F. R. Mayo, *J. Org. Chem.*,
1938, **3**, 33.

[88] M. S. Kharasch and (Mrs.) A. T. Read, *J. Amer. Chem. Soc.*, 1939, **61**,
3089; M. S. Kharasch, T. H. Chao, and H. C. Brown, *ibid.*, 1940, **62**, 2393.

mechanism is a chain reaction involving chlorine atoms and free radicals :

$$SO_2Cl_2 \longrightarrow SO_2 + Cl_2$$
$$Cl_2 + h\nu \longrightarrow 2Cl\cdot$$
$$Cl\cdot + RH \longrightarrow R\cdot + HCl$$
$$R\cdot + SO_2 \longrightarrow R\cdot SO_2\cdot$$
$$R\cdot SO_2\cdot + Cl_2 \longrightarrow R\cdot SO_2Cl + Cl\cdot$$
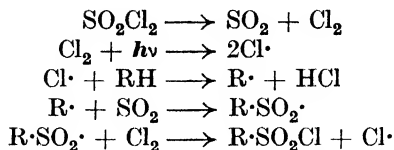
Photochemical reactions involving the COCl radical, derived from oxalyl chloride or carbonyl chloride, have also been reported.[89]

The participation of free radicals in reactions involving the abnormal addition of hydrogen bromide to olefins has been referred to in a recent Report [90] and a similar mechanism has now been put forward for the peroxide-catalysed addition of chlorine to ethylenic compounds by means of sulphuryl chloride.[91] In the former case the reaction chain is propagated by the bromine atom (a), in the latter case by the SO_2Cl radical (b), thus :

(a) $CH_2{:}CHBr + Br\cdot \longrightarrow CH_2Br\cdot CHBr\cdot$
$CH_2Br\cdot CHBr\cdot + HBr \longrightarrow CH_2Br\cdot CH_2Br + Br\cdot$

(b) $\cdot SO_2Cl \longrightarrow SO_2 + Cl\cdot$
$R_2C{:}CR_2 + Cl\cdot \longrightarrow R_2CCl\cdot CR_2\cdot$
$R_2CCl\cdot CR_2\cdot + SO_2Cl_2 \longrightarrow R_2CCl\cdot CR_2Cl + \cdot SO_2Cl$
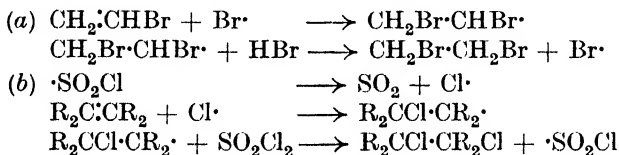
It is significant that these chain reactions are either photochemical processes or are initiated by means of benzoyl peroxide, the activity of which must be attributed to its decomposition into free radicals. The activity of benzoyl peroxide as a catalyst for the polymerisation of vinyl compounds can be ascribed to the same cause. Free radicals derived from the thermal decomposition of organometallic compounds are known to induce the polymerisation of unsaturated compounds and G. V. Schulz and G. Wittig [92] have shown that the addition of tetraphenylsuccinodinitrile (which dissociates reversibly into diphenylcyanomethyl radicals, $CN\cdot CPh_2\cdot$) to styrene results in an acceleration of the polymerisation process. The polymerisation of styrene is also accelerated by the addition of benzeneazotriphenyl-methane, which decomposes at 50—60° into triphenylmethyl, phenyl radicals and nitrogen.[93] These results indicate that the acceleration of polymerisation processes by means of benzoyl peroxide is not necessarily due to oxygen. R. G. W. Norrish and E. F. Brookman,[94] in an investigation on the co-polymerisation of

[89] M. S. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.*, 1940, **62**, 454.
[90] *Ann. Reports*, 1939, **36**, 219.
[91] M. S. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.*, 1939, **61**, 3432.
[92] *Naturwiss.*, 1939, **27**, 387.   [93] G. V. Schulz, *ibid.*, p. 659.
[94] *Proc. Roy. Soc.*, 1939, *A*, **171**, 147; see also R. G. W. Norrish, *Trans. Faraday Soc.*, 1939, **35**, 1087.

styrene and of methyl methacrylate, conclude that the reaction is initiated by free radicals derived from the catalyst and propagated by way of a free valency at the end of the extending chain as postulated by Staudinger. In this process they demonstrated that both chain branching and chain propagation may become limiting factors according to conditions, and on this basis were able to describe the rate of co-polymerisation in binary mixtures of various composition. One difficulty, which presents itself in any theory of polymerisation involving free radicals in the liquid phase, arises from the observation of H. Staudinger and A. Steinhofer [95] that the polymerisation of styrene in a solvent such as acetic acid, acetic anhydride, chloroform, methyl alcohol, or piperidine, results in no detectable reaction with the solvent molecules. Further discussion of the mechanism of polymerisation in solution is, however, beyond the scope of the present Report. D. H. H.

5. CAROTENOIDS.

The period under review has witnessed the publication of a volume of Beilstein's Handbook [1] containing a detailed account of the carotenoids. In this the literature has been covered up to the end of 1934, but many more recent references are quoted. M. T. Bogert has contributed an article on the carotenoids to Gilman's " Organic Chemistry " [2] and R. A. Morton [3] has discussed the constitution and physiological significance of the carotenoid pigments. The chromatographic separation and purification of carotenoids has been dealt with by L. Zechmeister and L. von Cholnoky [4] and microchromatographic methods for the detection, separation, and approximate estimation of small amounts of carotenoid pigments have been devised.[5]

Isomerisation of Carotenoids.

(a) *Hydrocarbons.*—The discovery and subsequent investigation of the spontaneous isomerisation of carotenoids in solution is perhaps the most significant development in this field in the period now being reviewed, especially since it has an important bearing on the technique employed in the isolation and manipulation of these labile pigments. Originally it was believed that the change was effected by

[95] *Annalen*, 1935, **517**, 47.

[1] Beilstein's "Handbuch der Organischen Chemie," XXX, Springer, Berlin, 1938.

[2] Wiley, New York; Chapman and Hall, London, 1938.

[3] *Chem. and Ind.*, 1940, **59**, 301.

[4] " Die chromatographische Adsorptionsmethode," Springer, Vienna, 1938.

[5] H. Willstaedt and T. K. With, *Z. physiol. Chem.*, 1938, **253**, 40.

the adsorption of carotene from light petroleum or benzene solutions on alumina; [6] L. Zechmeister and P. Tuzson,[7] however, made the important observation that the partial isomerisation of lycopene and β-carotene in solution is really spontaneous and independent of the adsorption process, the phenomenon being accelerated either by heating or by addition of iodine. Following this observation, G. P. Carter and A. E. Gillam [8] made a detailed examination of the behaviour of β-carotene, finding that chromatographically homogeneous material in light petroleum solution at room temperature is slowly converted (to the extent of about 30%) into an isomeric ψ-α-carotene, equilibrium being attained much more rapidly at 80°. Resolution of the mixture by adsorption yields unchanged β-carotene and the crystalline isomeride which in the location of its absorption maxima, adsorption affinity and vitamin-A activity closely resembles α-carotene; it is, however, optically inactive and in solution at 80° after ½ hour is reconverted (70%) into β-carotene. Isomerisation does not occur with crystalline β-carotene and to only a slight extent in petroleum solutions at 0°, but it would appear probable that in many of the cases where the occurrence of α-carotene has been reported, based solely on spectrographic and adsorption evidence, isomerisation induced by prolonged extraction processes at elevated temperatures may be partly or wholly responsible for the occurrence of this ψ-α-carotene. The complexity of the chromatogram, generally observed during the isolation of natural polyenes and previously attributed either to autoxidation, or to the presence of numerous pigments, is probably due to an appreciable extent to this isomerisation phenomenon, which appears to be quite general in the carotenoid series.

The behaviour of α-carotene on isomerisation [9] is rather bewildering, since the effect of heat on the solution is to produce a pigment, *neo*carotene, separable chromatographically from the more strongly adsorbed α-carotene and exhibiting maxima at shorter wave-lengths than the parent hydrocarbon. On attempted crystallisation, however, *neo*carotene changes to a crystalline *neo*-α-carotene, which is

$$\text{α-Carotene} \xrightarrow{\text{heat}} \textit{neo}\text{Carotene} \xrightarrow{\text{cryst.}} \textit{neo}\text{-α-Carotene}$$

| Abs. max. in CS_2 (A.) ... | 5080 | 5010 | 5090 |
| | 4770 | 4710 | 4765 |

quite different from either α-carotene or ψ-α-carotene, although similar to them in light absorption properties. Both ψ-α-carotene and *neo*-

[6] A. E. Gillam and M. S. El Ridi, *Biochem. J.*, 1936, **30**, 1735; A. E. Gillam, M. S. El Ridi, and S. K. Kon, *ibid.*, 1937, **31**, 1605.

[7] *Nature*, 1938, **141**, 249; *Biochem. J.*, 1938, **32**, 1305; *Ber.*, 1939, **72**, 1340.

[8] *Biochem. J.*, 1939, **33**, 1325.

[9] A. E. Gillam, M. S. El Ridi, and S. K. Kon, *loc. cit.*

α-carotene retain the provitamin A activities of the original β- and α-carotenes.

L. Zechmeister and P. Tuzson [7] described the formation of *neo*-lycopene, less strongly adsorbed and absorbing at shorter wave-lengths than lycopene itself. Attempts to obtain it crystalline,

	Lycopene $\longrightarrow$ *neo*Lycopene	
	5470	5360
Abs. max. in CS_2 (A.)	5050	4980
	4750	4660

however, always led to samples which showed no perceptible difference from ordinary lycopene, reminiscent of the behaviour of *neo*-carotene. The authors detected this reversible isomerisation, not only by spectrographic and chromatographic methods but also by observing the diminution in colour of the solution consequent upon the formation of *neo*lycopene.

(b) *Xanthophylls.**—H. H. Strain [10] observed that lutein and zeaxanthin were thermolabile in solution, that the subsequent chromatogram was complex, and that the new pigments produced in this way absorbed at shorter wave-lengths than the normal caro-tenoids. The isomerisation of xanthophylls has been studied in some detail by Zechmeister and his collaborators [11] who find that, while the light absorption maxima of isomerised carotenoids are displaced to shorter wave-lengths, in striking contrast to the be-haviour of the epiphasic pigments, the pronouncedly hypophasic carotenoids are converted into more than one isomeride, all of these being adsorbed more strongly than the parent pigments. Isomeris-ation of zeaxanthin with iodine in benzene solution [12] yields crystalline *neo*zeaxanthins *A*, *B*, and *C*, of which the first two, particularly *neo*zeaxanthin *A*, differ appreciably in optical rotation from the parent xanthophyll. The ester *neo*physalien, obtained by isomeris-ation of physalien, the dipalmitate of zeaxanthin, exhibits less change in this respect.

The Nature of the Isomerism.—This problem has been discussed by both Zechmeister and Gillam [13] and the theory that the isomerism is to be attributed to double bond shift may be discarded, especially

[10] "Leaf Xanthophylls," Carnegie Institute of Washington Publication No. 490, 1938.

[11] L. Zechmeister and P. Tuzson, *Ber.*, 1939, **72,** 1340; L. Zechmeister, L. von Cholnoky, and A. Polgár, *ibid.*, p. 1678; L. Zechmeister and L. von Cholnoky, *Annalen*, 1940, **543,** 248.

[12] L. Zechmeister, L. von Cholnoky, and A. Polgár, *Ber.*, 1939, **72,** 1678.

[13] See also G. Mackinney, *Ann. Rev. Biochem.*, 1940, **9,** 474.

* Oxygenated carotenoids, other than the polyene carboxylic acids, are termed xanthophylls. The name lutein, rather than xanthophyll, is employed for the main hypophasic pigment of green leaves.

since β-carotenone, in which no such movement is possible on the accepted formula, is isomerised under the usual conditions.[12]   The alternative theory of geometrical isomerism receives support in that the observed differences between the isomerides are essentially physical, no chemical or biological differences having as yet been observed.

The polyene acids, bixin and crocetin and their derivatives, have long been known to exist in *cis*- and *trans*-forms [14] although the reconversion of the stable *trans*- into the labile *cis*-forms has not yet been effected.   It is interesting to note that these forms are separable chromatographically [15] and especially that the more labile *cis*-isomerides exhibit absorption maxima somewhat displaced towards the ultra-violet, the displacements being comparable with those observed with the isomerised carotenoids (see Table, Chloroform solutions).*

	Crocetin dimethyl ester.[16]		Bixin methyl ester [15] (Norbixin dimethyl ester).			β-Carotene.[7]	
trans-	4630	4345	5095	4755	4440	4910	4630
cis-	4580	4325	5030	4700	4410	(ψ-α-) 4860	4560 A.

Assuming that the carotenoids normally exist in the most elongated form with *trans-trans* linkages, it is obvious that geometrical isomerism, depending of course on the position in the chain of the affected ethenoid linkage, will alter considerably the shape of the molecule.   This might be apparent in the X-ray spectra of the isomerides.   R. S. Mulliken,[17] examining the absorption spectra of carotenoids from the quantum-mechanical aspect, concludes that " the more elongated the molecule the more the intensity should be confined to the long wave-length end of the spectrum and the more intense should be the colour."   The observation [7] that the isomerisation of lycopene is accompanied by a diminution in colour intensity, and the considerably lower intensity of light absorption of heat-treated zeaxanthin solutions,[18] it being observed in the latter case that the intensity decrease is greater at the longer wave-lengths, would thus appear to be in agreement with the *cis-trans*-explanation.

[14] R. Kuhn and A. Winterstein, *Ber.*, 1932, **65**, 646.

[15] *Idem, ibid.*, p. 646; A. Winterstein, "Handbuch Pflanzenanalyse," 1934, **4**, 1414.

[16] R. Kuhn and A. Winterstein, *Ber.*, 1933, **66**, 209.

[17] *Science*, 1939, **89**, 389; *J. Chem. Physics*, 1939, **7**, 364.

[18] H. H. Strain, " Leaf Xanthophylls," Carnegie Institute of Washington Publication No. 490, 1938, 112.

* Similar displacements in the absorption maxima and marked differences in intensity are observed with the *cis*- and *trans*-isomers of stilbene and cinnamic acid (K. Dimroth, *Angew. Chem.*, 1939, **52**, 545).

Stepwise Degradation of Carotenoids.

Karrer and his collaborators, in a series of interesting papers, have described the isolation of a number of polyene aldehydes from β-carotene and other carotenoids by oxidation under carefully controlled conditions with alkaline permanganate.   This work has provided further evidence for the correctness of the accepted formulæ for the carotenoids and has thrown valuable light on the relationship between structure and provitamin A activity (q.v.).   Oxidation of β-carotene (I) itself yields a mixture of products,[19] from which β-apo-2-carotenal,* $C_{30}H_{40}O$ (II), and β-apo-4-carotenal,* $C_{25}H_{34}O$
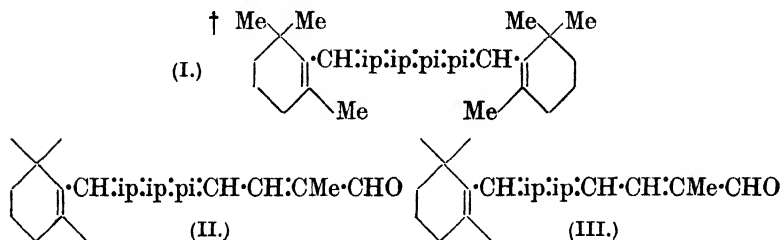
(III), have been obtained, the former as a crystalline solid and the latter as an oil, readily separated from one another by chromatographic resolution on calcium hydroxide.   These aldehydes have been characterised by the preparation of oximes and semicarbazones, their constitutions are based on analytical and spectrographic data, and it is noteworthy that the absorption spectrum of (II) (and its oxime) is practically identical with that of β-citraurin (q.v.) (and its oxime) [20] which is probably a 3-hydroxy-β-apo-2-carotenal (this was subsequently confirmed by the observation of P. Karrer, A. Rüegger, and U. Solmssen [21] that some β-citraurin is produced on oxidative degradation of zeaxanthin diacetate).   β-apo-3- and β-apo-5-Carotenals are also formed in this degradation, but the yields of these products were too small to permit of complete characterisation.[22]

β-apo-Carotenals are not obtained by degradation of α-carotene,[22]

[19] P. Karrer and U. Solmssen, Helv. Chim. Acta, 1937, 20, 682; P. Karrer, U. Solmssen, and W. Gugelmann, ibid., p. 1020.

[20] L. Zechmeister and P. Tuzson, Ber., 1936, 69, 1878.

[21] Helv. Chim. Acta, 1938, 21, 448.

[22] H. von Euler, P. Karrer, and U. Solmssen, ibid., p. 211.

* " Apo-n-" indicates fission at the nth double bond from the end of the unsaturated system.

† The convenient abbreviation, due to R. A. Morton (Nature, 1940, 145, 286), of the four isoprene units of the central polyene chain of the carotenoids to :ip:ip:pi:pi: has been adopted throughout this report. " ip " is thus equivalent to CH·CMe:CH·CH

the β- rather than the α-ionone ring being attacked preferentially *
to yield an α-*apo*-2-carotenal (IV) exhibiting absorption maxima at
somewhat shorter wave-lengths than the corresponding β-aldehyde

(IV.) $\cdot$CH:ip:ip:pi:CH·CH:CMe·CHO
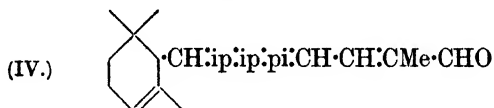
(II). The displacements are equivalent to those observed between
the maxima of the α- and β-carotenes. The absorption spectra of
these carotenals and their derivatives, as well as those of the caro-
tenols obtained from them on reduction with aluminium *iso*propoxide,
are valuable in that they provide data for chromophores intermediate
between those of the natural carotenoids and vitamin A and its
analogues.

In addition to the lycopenal (VI) and bixindialdehyde (VIII)
previously isolated by R. Kuhn and C. Grundmann [23] by oxidation
with chromic acid, permanganate degradation of lycopene (V),[24]

$$\overset{\text{Me}}{\text{CMe}_2\text{:CH·CH}_2\text{·CH}_2\text{·C:CH·CH:ip:ip:pi:pi:CH·CH:CMe·CH}_2\text{·CH}_2\text{·CH:CMe}_2}$$
(V.)

(VI.) CMe_2:CH·CH$_2$·CH$_2$·CMe:CH·CH:ip:ip:pi:pi:CH·CHO

(VII.) CMe_2:CH·CH$_2$·CH$_2$·CMe:CH·CH:ip:ip:pi:CH·CH:CMe·CHO

OHC·CH:ip:ip:pi:pi:CH·CHO   OHC·CH:ip:ip:pi·CH·CH:CMe·CHO
        (VIII.)   (IX.)
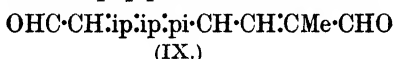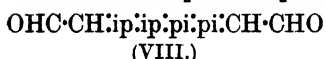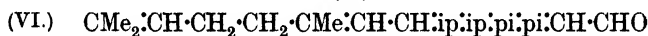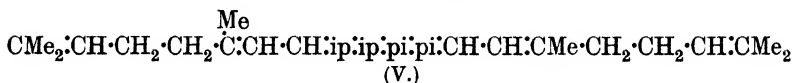
followed by resolution of the products on calcium hydroxide, yields
apo-3-lycopenal (VII) and *apo*-1-bixindialdehyde (IX). The con-
stitutions given for the latter aldehydes are based on their absorption
spectra, the differences from (VI) and (VIII) respectively correspond-
ing to the depletion of the conjugated system by one double bond.

Interesting results have been obtained by permanganate degrad-
ation in the bixin series.[25]   Oxidation of labile bixin methyl ester

R·CH:CH·CH:CMe·CH:CH·CO$_2$Me   R·CH:CH·CH:CMe·CHO
        (X.)   (XI.)

(XII.) R·CH:CH·CHO   R·CHO   (XIII.)
        R = CO$_2$Me·CH:ip:ip:CH·CH:CMe
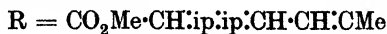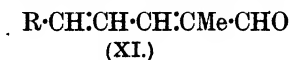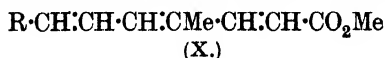
(labile norbixin methyl ester) (X) yields the three aldehyde-esters,
(XI), (XII), and (XIII), the first two being labile and converted by

[23] *Ber.*, 1932, **65**, 898, 1880.
[24] P. Karrer and W. Jaffé, *Helv. Chim. Acta*, 1939, **22**, 69.
[25] P. Karrer and U. Solmssen, *ibid.*, 1937, **20**, 1396.

* This greater stability of the α-ionone ring is evident also in the behaviour
of α-carotene on oxidation with chromic anhydride (P. Karrer, H. von Euler,
and U. Solmssen, *Helv. Chim. Acta*, 1934, **17**, 1169).

treatment with iodine into the coresponding stable aldehyde-esters, also obtained by the similar degradation of stable bixin methyl ester. Since the same *apo*-3-norbixinal methyl ester (XIII) is a product of the degradation of both labile (*cis*-) and stable (*trans*-) bixin esters, Karrer and Solmssen conclude that the isomerism of the bixins depends on geometrical isomerism around the third ethenoid linkage from the end of the chain.   It is considered improbable that a highly labile *apo*-3-norbixinal methyl ester (XIII) is converted into the stable form during the oxidation of labile bixin methyl ester.

Closely analogous to the behaviour of α-carotene, oxidative degradation of the diacetate of lutein (XIV) [26] results in fission of the β-ionone ring, yielding mainly a new (α-) citraurin (XV), similar in light absorption properties to α-*apo*-2-carotenal (IV), only a trace of the β-aldehyde being formed.   In addition to the β-(ordinary)

(XIV.)   HO⟨⟩·CH:ip:ip:pi:pi:CH·⟨⟩OH

(XV.)   HO⟨⟩·CH:ip:ip:pi:CH·CH:CMe·CHO
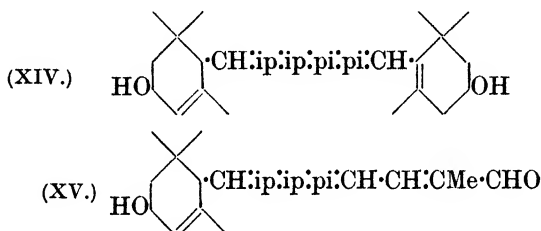
citraurin (*apo*-2-zeaxanthinal) already mentioned, oxidation of the β-carotene analogue, zeaxanthin, yields some *apo*-4-zeaxanthinal.[21]

Although R. Kuhn and H. Brockmann [27] oxidised the methyl ester of azafrin with chromic acid to obtain two acyclic azafrinal methyl esters, $C_{15}H_{18}O_3$ and $C_{13}H_{16}O_3$, oxidation with alkaline permanganate [28] fails to yield products of high molecular weight.   Rather surprisingly the free acid is smoothly degraded with the loss of only two carbon atoms to *apo*-1-azafrinal (XVI).

(XVI.)   ⟨⟩OH / ·CH:ip:ip:CH·CH:CMe·CHO / OH
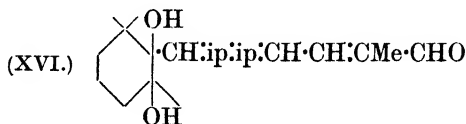
The diphenyl polyenes are more stable than the carotenoids to oxidative degradation, but, employing acid permanganate, P. Karrer and H. Obst [29] have degraded αβ-diphenyloctatetraene (XVII) to

[26] P. Karrer, H. Koenig, and U. Solmssen, *Helv. Chim. Acta*, 1938, **21**, 445.
[27] *Annalen*, 1935, **516**, 95.
[28] P. Karrer, H. Obst, and U. Solmssen, *Helv. Chim. Acta*, 1938, **21**, 451.
[29] *Ibid.*, 1939, **22**, 1191.

benzaldehyde and an α-phenylheptatrien-ζ-al (XVIII), the latter
being probably a stereoisomer of the phenylheptatrienal previously
described.[30]

$$\text{Ph·[CH:CH]}_4\text{·Ph} \longrightarrow \text{Ph·[CH:CH]}_3\text{·CHO} + \text{Ph·CHO}$$
$$\text{(XVII.)} \qquad\qquad\qquad \text{(XVIII.)}$$
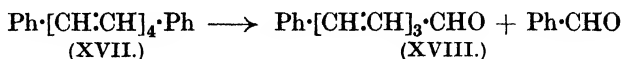
Constitution and Provitamin A Activity.

The work of Karrer and his collaborators on the stepwise degrada-
tion of α- and β-carotenes and of Heilbron and his school on the
transformation products of vitamin A has provided further informa-
tion concerning the relationship between chemical constitution and
vitamin A activity. These results, together with those obtained
earlier, are in the accompanying table of physiologically active
substances.

Naturally occurring carotenoids.

a-, β-, and γ-Carotenes	Aphanin[33]	Myxoxanthin[34]
Cryptoxanthin[31]	Aphanicin[33]	Leprotene[35]
Echinenone[32]		

Polyenes derived from naturally occurring carotenoids.

Di-iodo-a- and -β-carotenes[36]   ψ-a-Carotene[6]
β-Carotene oxide[37]   neoCarotene[6]
β-Hydroxycarotene[38]   neo-a-Carotene[6]
Semi-β-carotenone and its oxime[39]   β-apo-2-Carotenal and its oxime[42]
Anhydrosemi-β-carotenone[40]   Carbinol from β-apo-2-carotenal and
Product from lutein or zeaxanthin   EtMgBr[43]
   with PBr₃[41]   β-apo-4-Carotenal oxime[22]

[30] R. Kuhn and A. Winterstein, *Helv. Chim. Acta*, 1928, **11**, 87.

[31] R. Kuhn and C. Grundmann, *Ber.*, 1934, **67**, 593.

[32] E. Lederer and T. Moore, *Nature*, 1936, **137**, 996.

[33] A. Scheunert and K. H. Wagner, *Z. physiol. Chem.*, 1938, **20**, 272.

[34] I. M. Heilbron and B. Lythgoe, *J.*, 1936, 1376.

[35] Y. Takeda and T. Ohta, *Z. physiol. Chem.*, 1939, **258**, 6.

[36] H. von Euler, P. Karrer, and M. Rydbom, *Ber.*, 1929, **62**, 2445;
P. Karrer, U. Solmssen, and O. Walker, *Helv. Chim. Acta*, 1934, **17**, 417.

[37] H. von Euler, P. Karrer, and O. Walker, *Helv. Chim. Acta*, 1932, **15**, 1507.

[38] R. Kuhn and H. Brockmann, *Z. physiol. Chem.*, 1932, **213**, 1; *Ber.*, 1934, **67**, 1408; *Annalen*, 1935, **516**, 95.

[39] *Idem, Ber.*, 1932, **65**, 894; 1933, **66**, 1319; *Annalen*, 1935, **516**, 95.

[40] *Idem, Annalen*, 1935, **516**, 95.

[41] H. von Euler, P. Karrer, and A. Zubrys, *Helv. Chim. Acta*, 1934, **17**, 24.

[42] H. von Euler, G. Günther, M. Malmberg, and P. Karrer, *ibid.*, 1938, **21**, 1619; H. von Euler, P. Karrer, and U. Solmssen, *ibid.*, p. 211; P. Karrer and U. Solmssen, *ibid.*, 1937, **20**, 682.

[43] H. von Euler, G. Günther, M. Malmberg, and P. Karrer, *ibid.*, 1938, **21**, 1619; P. Karrer, A. Rüegger, and A. Geiger, *ibid.*, p. 1171.

The natural vitamins and derived products.

Vitamin A	C_{20}-Aldehyde oxime [46]
Vitamin A$_2$ [44]	C_{23}-Ketone from oxidative condens-
C_{20}-Aldehyde from the oxidation of	ation of vitamin A with acetone [47]
vitamin A [45]	Corresponding C_{23}-alcohol [47]
Corresponding C_{20}-alcohol [45]	

The presence of an unsubstituted β-ionone ring in the molecule is one of the necessary conditions for biological activity. The acyclic hydrocarbon, lycopene, and the naturally occurring xanthophylls are inactive, but cryptoxanthin (XIX), in which only one of its two β-ionone rings carries a hydroxyl group, functions as a provitamin,

HO⟨⟩·CH:ip:ip:pi:pi:CH·⟨⟩   (XIX.)   HO⟨⟩·CH:ip:ip:pi:pi:CH·⟨⟩   (XX.)
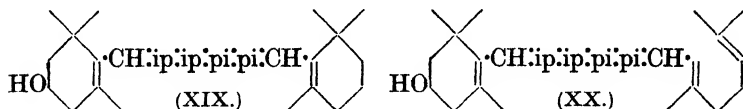
whereas the monocyclic rubixanthin (XX) is inactive. So many examples of this specificity are available that the failure of a caro- tenoid to promote animal growth is frequently interpreted to indicate the absence of an unmodified β-ionone ring.

The aldehydes β-*apo*-2- and β-*apo*-4-carotenal, from the perman- ganate degradation of β-carotene, as well as the carbinol produced by the action of ethylmagnesium bromide on the former, act as provitamins A. The C_{23}-ketone, axerophthylideneacetone (XXI), obtained by the oxidation of vitamin A with aluminium *tert.*- butoxide in the presence of acetone, and the secondary alcohol derived from it by Ponndorf reduction are also active. That the

(XXI.)   ⟨⟩·CH:ip:ip:CH·CO·CH$_3$
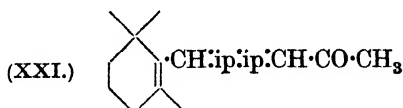
biological activity of such substances is due to their degradation to vitamin A in the animal and not to any inherent properties of the substances themselves, has been demonstrated by H. von Euler, G. Günther, M. Malmberg, and P. Karrer,[42] who showed that ad- ministration of massive doses (50γ) of β-*apo*-2-carotenal to young rats

[44] A. E. Gillam, I. M. Heilbron, W. E. Jones, and E. Lederer, *Biochem. J.*, 1937, **32**, 1938.

[45] E. Haworth, I. M. Heilbron, W. E. Jones, A. L. Morrison, and J. B. Polya, *J.*, 1939, 128.

[46] Private communication from Professor I. M. Heilbron.

[47] J. W. Batty, A. Burawoy, S. H. Harper, I. M. Heilbron, and W. E. Jones, *J.*, 1938, 175; I. M. Heilbron, A. W. Johnson, and W. E. Jones, *J.*, 1939, 1560. Contrary to the earlier results, more recent determinations have shown these compounds to be active (private communication from Professor I. M. Heilbron).

results in an accumulation of vitamin A in the liver. As was expected, α-*apo*-2-carotenal was found to be inactive.[22]

The fact that ψ-α-carotene, *neocarotene* and *neo*-α-carotene are all biologically active would appear to disprove the theory that displacement of a double bond from the conjugated system occurs in the isomerisation of the carotenoids.

Plant Carotenoids.

Leaf Xanthophylls.—In a comprehensive memoir on the leaf xanthophylls H. H. Strain [10] has made an extremely valuable contribution to our knowledge not only of a field so vitally connected with photosynthesis, but also of the manipulation and separation of complex mixtures of labile carotenoids. Contrary to the findings of earlier workers in this field Strain has been able to show that normal green leaves contain at least twelve xanthophylls, in approximately the same proportions in all the leaves examined. Previous workers had failed to extract a number of more soluble xanthophylls, containing more than two hydroxyl groups, from the aqueous acetone or alcoholic solutions, obtained after phase separation. Lutein (XIV) represents more than half the xanthophyll mixture, in which small amounts of cryptoxanthin and zeaxanthin * are always present.[48]

Lycoxanthin and Lycoxanthophyll.—Accompanying lycopene in the fruits of various members of the *Solanaceæ*, *Solanum dulcamara* (nightshade) being the richest source, are small quantities of two xanthophylls of a novel type.[49] Lycoxanthin, $C_{40}H_{56}O$, and lycoxanthophyll, $C_{40}H_{56}O_2$, characterised by the preparation of a monoacetate and a dipalmitate respectively, exhibit absorption maxima identical with those of lycopene and on this and other evidence, including comparative adsorption affinity, it is concluded that they are the hitherto unknown hydroxylycopenes, bearing the same relationship to the parent hydrocarbon as cryptoxanthin and zeaxanthin bear to β-carotene. One of the pigments of the fungus *Polystigma rubrum* is probably lycoxanthin.[50]

Capsanthin.—Further evidence for the constitution of this paprika pigment [51] has been accumulated by L. Zechmeister and L. von Cholnoky,[52] by the degradation of the diacetate with chromic

[48] See also H. Kylin, *K. fysiogr. Sällsk. Lund Forh.*, 1939, **9**, 1.

[49] L. Zechmeister and L. von Cholnoky, *Ber.*, 1936, **69**, 422.

[50] E. Lederer, *Bull. Soc. Chim. biol.*, 1938, **20**, 611.

[51] *Ann. Reports*, 1935, **32**, 301.   [52] *Annalen*, 1936, **523**, 101.

* All the specimens of the latter pigment, despite rigorous purification remained lævorotatory in agreement with the results obtained by L. Zechmeister, L. von Cholnoky, and A. Polgár [12] but in contradiction to the earlier findings of R. Kuhn and C. Grundmann (*Ber.*, 1934, **67**, 596; *Ann. Reports*, 1935, **32**, 291).

acid to products analogous to those obtained by R. Kuhn and H. Brockmann [53] in their classic oxidation of β-carotene. Under mild conditions capsanthin (XXII) yields capsanthinone (XXIII),
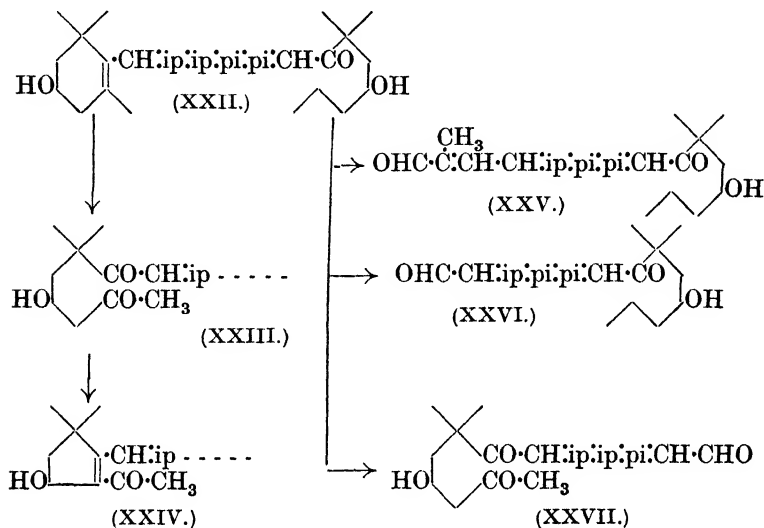
$C_{40}H_{58}O_4$, resembling semi-β-carotenone in its cyclisation with alkali to anhydrocapsanthinone (XXIV), $C_{40}H_{58}O_4$, the latter reaction providing evidence of the position of the hydroxyl group in the β-ionone ring. Capsanthylal (XXV), $C_{30}H_{42}O_3$, capsylaldehyde (XXVI), $C_{27}H_{38}O_3$, and 4-hydroxy-β-carotenonealdehyde (XXVII), $C_{27}H_{36}O_4$, are simultaneously produced by more vigorous oxidation of (XXII). While these degradations leave little doubt as to the constitution of the cyclic portion of the capsanthin molecule, no conclusive information concerning the acyclic end is yet available. P. Karrer and H. Hübner [54] have reduced capsanthin with aluminium isopropoxide to capsanthol. This contains ten double bonds (hydrogenation) and since its absorption maxima are displaced some 350 A. towards the ultra-violet as compared with those of capsanthin, the carbonyl groups of the latter must be conjugated with the ten double-bonded polyene chain.

Citraurin.—From the complex mixture of carotenoids occurring in the orange (*Citrus aurantius*), in addition to cryptoxanthin, violaxanthin and a mixture of zeaxanthin and lutein, a polyene hydroxy-aldehyde, citraurin, has been isolated.[55] It occurs in the tissue in esterified form and is the first naturally occurring polyene

[53] *Annalen*, 1935, **516**, 95.   [54] *Helv. Chim. Acta*, 1936, **19**, 474.
[55] L. Zechmeister and P. Tuzson, *Ber.*, 1936, **69**, 1878; 1937, **70**, 1966.

aldehyde to be discovered. Analyses of the aldehyde and of its crystalline oxime indicate a formula $C_{30}H_{40}O_2$, and it is suggested that it is formed by degradation of zeaxanthin or other xanthophyll in the ripening fruit. Its constitution (XXVIII) was readily established by the remarkable production of the aldehyde on fission of capsanthin (XXII) with aqueous alcoholic alkali,[56] analogous in

(XXII.) $\longrightarrow$ HO⟨⟩·CH:ip:ip:pi:CH·CH:CMe·CHO   (XXVIII.)

some respects to the fission of citral to methylheptenone. Further confirmation of the structure was provided by the observation [57] that the absorption spectrum of citraurin is identical with that of β-apo-2-carotenal and later that citraurin (β-citraurin) is a product of the permanganate degradation of zeaxanthin.[21] The only other conversion of one naturally occurring carotenoid into another in the laboratory is that of rhodoxanthin into zeaxanthin.[58]

Dehydro-β-carotene (iso*Carotene*).—P. Karrer and G. Schwab [59] have reconsidered the constitution of " isocarotene," the hydrocarbon obtained on treatment of the tetraiodide of β-carotene with acetone.[60] The evidence on which their representation of " isocarotene " as a dehydro-β-carotene (XXIX) is based is as follows : [61] The analytical data for this biologically inactive hydrocarbon agree with

(XXIX.) [⟨⟩:CH·CH:CMe·CH:CH·CH:CMe·CH:CH·]₂
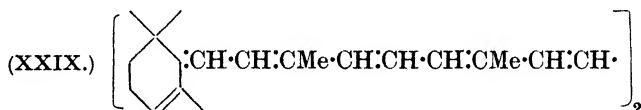
a formula $C_{40}H_{54}$ and all twelve double bonds are conjugated. Since ozonolysis gives neither geronic acid nor *iso*geronic acid, the rings cannot be of the normal β- or α-ionone type, and the failure to isolate either *iso*hexoic acid or aldehyde from this product dismisses the possibility of an open-chain structure. The permanganate degradation of " isocarotene " is abnormal, giving no aldehydes of the type of β-apo-2-carotenal, and more vigorous oxidation yields only αα-dimethylglutaric acid. The proposed structure (XXIX) allows of a simple explanation of its formation from the tetraiodide.

β-*Dihydrocarotene*.—P. Karrer and A. Rüegger [62] have succeeded

[56] L. Zechmeister and L. von Cholnoky, *Annalen*, 1937, **530**, 291.
[57] P. Karrer and U. Solmssen, *Helv. Chim. Acta*, 1937, **20**, 682.
[58] P. Karrer and U. Solmssen, *Helv. Chim. Acta*, 1935, **18**, 477.
[59] *Ibid.*, 1940, **23**, 578.
[60] R. Kuhn and E. Lederer, *Ber.*, 1932, **65**, 637.
[61] P. Karrer, K. Schöpp, and R. Morf, *Helv. Chim. Acta*, 1932, **15**, 1158.
[62] *Ibid.*, 1940, **23**, 955.

in preparing small quantities of a crystalline β-dihydrocarotene by reduction of β-carotene with aluminium amalgam. The dihydro-compound was previously obtained as an oil which exhibited biological activity,[63] whereas the crystalline material now obtained is inactive. This fact, and the light absorption of the β-dihydrocarotene, which is characteristic for a system of eight conjugated double

(XXX.) $\left[\underset{\diagup}{\overset{\diagup}{\bigtimes}}\cdot CH_2\cdot CH\!:\!CMe\cdot CH\!:\!CH\cdot CH\!:\!CMe\cdot CH\!:\!CH\cdot\right]_2$
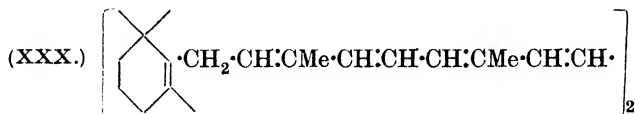
bonds, suggest that the reduction product has the constitution (XXX).

The Algæ.—That certain plant carotenoids function as provitamins A has long been appreciated, and it is probable that leaf carotene acts as a sensitiser for the photo-oxidation of the plant growth hormone auxin in causing phototaxis.[64] Many, as yet unsuccessful, attempts have been made to establish the precise function of the leaf xanthophylls and carotenes in plant economy,[65] and it is generally recognised that carotenoid pigments are involved in the phenomenon of vision.[66] Yet another important rôle played by these pigments in biological processes has been revealed recently. In a series of brilliant researches, Kuhn and Moewus and their collaborators [67] have demonstrated conclusively that derivatives of the naturally occurring polyene acid, crocetin (XXXI), control the processes involved in the copulation of certain algal gametes. Useful summaries of this work have been given by R. Kuhn [68] and F. Moewus.[69] A detailed account does not come within the scope of this Report, but certain of the outstanding features can be indicated.

(XXXI.) $HO_2C\cdot CMe\!:\!CH\cdot CH\!:\!ip\!:\!pi\!:\!CH\cdot CH\!:\!CMe\cdot CO_2H$

The inactive gametes of the unicellular green alga *Chlamydomonas eugametos f. simplex* develop cilia and become motile on irradiation.

[63] H. von Euler, P. Karrer, H. Hellström, and M. Rydbom, *Helv. Chim. Acta,* 1931, **14**, 839.

[64] E. Bunning, *Planta,* 1938, **27**, 148, 583.

[65] Summaries : H. H. Strain, " Leaf Xanthophylls," Carnegie Institute of Washington Publication No. 490, 1938; J. H. C. Smith, *Ann. Rev. Biochem.,* 1937, **6**, 494.

[66] G. Wald, *J. Gen. Physiol.,* 1935, **19**, 351; *Nature,* 1934, **134**, 65; 1937, **139**, 1017; **140**, 545; *J. Biol Chem.,* 1938, **122**, 449; R. Lemberg, *Ann. Rev. Biochem.,* 1938, **7**, 438; P. Karrer and W. Straus, *Helv. Chim. Acta,* 1938, **21**, 1624.

[67] F. Moewus, *Jahrb. wiss. Bot.,* 1938, **86**, 753; *Arch. Protistenkunde,* 1939, **92**, 485; R. Kuhn, F. Moewus, and D. Jerchel, *Ber.,* 1938, **71**, 1541; R. Kuhn, F. Moewus, and G. Wendt, *Ber.,* 1939, **72**, 1702; R. Kuhn and F. Moewus, *Ber.,* 1940, **73**, 547.

[68] *Angew. Chem.,* 1940, **53**, 1.   [69] *Naturwiss.,* 1939, **27**, 97.

Kuhn and Moewus have shown that this motility is brought about by the secretion of crocin (XXXII), the saffron pigment, into the solution, since motility can be induced in the dark by employing exceedingly minute amounts of the glycoside, approximately in the proportion of one molecule of crocin to each gamete.

$$\begin{array}{cc}
\text{CH}_2\text{·O·CH·[CH·OH]}_3\text{·CH·CH}_2\text{·OH} & \text{CH}_2\text{·O·CH·[CH·OH]}_3\text{·CH·CH}_2\text{·OH} \\
\end{array}$$

CH₂·O·CH·[CH·OH]₃·CH·CH₂·OH   CH₂·O·CH·[CH·OH]₃·CH·CH₂·OH
⌐─ĊH   └────O────┘   ⌐─ĊH   └────O────┘
O [ĊH·OH]₃   O [ĊH·OH]₃
└─ĊH   └─ĊH
 Ö   Ö
ĊO·CMe:CH·CH:ip:pi:CH·CH=CMe—ĊO
                    (XXXII.)
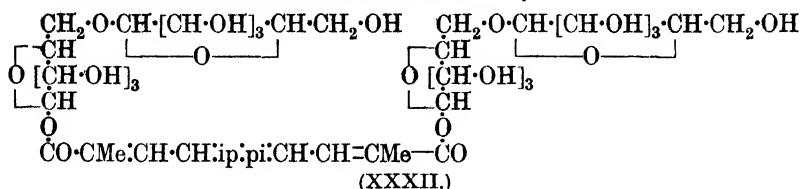
Crocin (crocetin digentiobioside) is capable of rendering gametes motile in the dark at the amazing dilution of 1 in 250,000,000,000,000 (1 in $2 \cdot 5 \times 10^{14}$) and this remarkably sensitive test has been employed to indicate the presence of the pigment in the sexual organs of lilies, tulips and other flowers,[70] leading to the speculation that crocin also has a function in the fertilisation processes of the higher plants.

Further irradiation of the now motile gametes with blue or violet light (red is ineffective) results in the activation (for copulation) first of the female gametes, then, after a time, of the male gametes and consequent copulation. That these processes are dependent on the liberation of *cis*-crocetin dimethyl ester (V) from the cells and its gradual transformation in blue or violet light into the *trans*-ester (k_0) [71] has been proved by their reproduction in the dark when synthetic mixtures of the geometrical isomers are employed.[72] Under these conditions the activation of the female gametes ensues

$$
\begin{array}{cccccc}
V & \longrightarrow & k_\female & \longrightarrow & k_\male & \longrightarrow & k_0 \\
cis\text{-} & & 3\ cis\text{-} : & & 1\ cis\text{-} : & & trans\text{-} \\
& & 1\ trans\text{-} & & 3\ trans\text{-} & &
\end{array}
$$
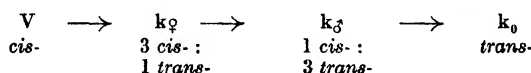
with a 75% *cis* : 25% *trans* mixture ($k_\female$) and of the male gametes with the complementary mixture ($k_\male$), the final irradiation product, the *trans*-ester (k_0), being without influence on either male or female gametes. This action is highly specific, for not only are *cis*- and *trans*-mixtures of crocetin and its diethyl ester both inactive, but other strains of *Chlamydomonas eugametos* require different proportions of the isomers for activation (*e.g.*, for *Chlamydomonas Braunii* $k_\female$ is 95% *cis* : 5% *trans*), the male proportion ($k_\male$) always being complementary to the female ($k_\female$).

Since geometrical isomerism in the crocetin series is of such

[70] F. Moewus, *Biol. Zentr.*, 1940, **60**, 142.

[71] Readily effected in the laboratory; R. Kuhn and A. Winterstein, *Ber.*, 1933, **66**, 209.

[72] See, however, R. Kuhn and F. Moewus, *Ber.*, 1940, **73**, 559.

fundamental physiological importance, it is possible that the recently discovered isomerisation phenomenon in other carotenoids is not without some biological significance.

The earlier work of Heilbron and his co-workers [73] on the algal lipochromes has been rendered more complete by the publication of the results of an extensive study of these pigments in a comprehensive memoir.[74] Since crystalline pigments were isolated wherever possible, this survey is of real significance as compared with studies of a purely qualitative nature.[75]

As is implied in the botanical classification of the algæ, members of the same class, irrespective of order or family, were found to exhibit a marked uniformity in carotenoid pigmentation. Carotene is ubiquitous and common to all the algæ, but each class possesses one or more characteristic xanthophylls. In the Phæophyceæ complete uniformity was observed, fucoxanthin being found in all the members examined. This homogeneity was further emphasised by the fact that fucosterol was found to be the major sterol constituent of this class. The Chlorophyceæ approximate more closely to the higher plants than any other algal class in synthesising only carotene and lutein. Exceptions were observed in *Zygnema pectinatum* and *Vaucheria hamata*, which also contained fucoxanthin and violaxanthin respectively. Fucoxanthin and lutein are present both in the Chrysophyceæ and the Bacillariophyceæ and flavoxanthin was shown to be the main xanthophyll in *Botrydium granulatum*, the only member of the Xanthophyceæ examined. The carotenoids of the Rhodophyceæ are essentially carotene and lutein, but the purple *Polysiphonia nigrescens* is exceptional in that it also contains fucoxanthin. The Myxophyceæ (Cyanophyceæ) are unique in containing in addition to carotene and lutein, the epiphasic myxoxanthin. Myxoxanthophyll and other hypophasic pigments occur in *Oscillatoria rubescens*. Other workers [76] have made a quantitative study of the relative amounts of chlorophyll and carotenoids in the various classes of algæ.

Oscillatoria rubescens is a good source of the ketone myxoxanthin,[77] $C_{40}H_{54}O$, the structure (XXXIII) suggested for which being based on the following facts : Myxoxanthin has twelve ethenoid linkages

[73] I. M. Heilbron and R. F. Phipers, *Biochem. J.*, 1935, **29,** 1369; I. M. Heilbron, E. G. Parry, and R. F. Phipers, *ibid.*, p. 1376.

[74] P. W. Carter, I. M. Heilbron, and B. Lythgoe, *Proc. Roy. Soc.*, 1939, *B*, **128,** 82.

[75] H. Kylin, *Z. physiol. Chem.* 1927, **166,** 39; *K. fysiogr. Sällsk. Lund Forh.*, 1937, **7,** 119.

[76] A. Seybold and K. Egle, *Jahrb. wiss. Bot.*, 1938, **86,** 50.

[77] I. M. Heilbron, B. Lythgoe, and R. F. Phipers, *Nature*, 1935, **136,** 989; I. M. Heilbron and B. Lythgoe, *J.*, 1936, 1376.

and its single ring must be of the β-ionone type to account for its physiological activity. Since the oxime absorbs at some 100 A. to

(XXXIII.) [chemical structure diagram: ·CH:ip:ip:pi:pi:CH· with O]
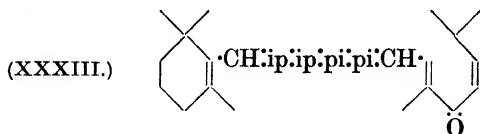
longer wave-lengths than the ketone, and myxoxanthol, the aluminium *iso*propoxide reduction product, is spectroscopically identical with γ-carotene and rubixanthin (eleven conjugated double bonds), then the carbonyl group must be associated with the conjugated system. The peculiar single-banded light absorption of myxoxanthin is atrributed to the simultaneous conjugation of the twelfth ethenoid linkage with the carbonyl group. The hypophasic pigments of the alga consist essentially of lutein and the new myxoxanthophyll, $C_{40}H_{56}O_7$ (abs. max. in chloroform, 5180, 4845, and 4500 A.), which, unlike most known xanthophylls, is strongly lævorotatory.

Tischer has examined the carotenoids of a number of fresh water algæ and from the blue alga *Aphanizomenon flos-aquæ*, another member of the Myxophyceæ, β-carotene and four new pigments have been isolated.[78] The epiphasic, optically inactive aphanin, $C_{40}H_{54}O$, contains eleven ethenoid linkages, and, like myxoxanthin, is ketonic. The carbonyl group is isolated, however, since the absorption spectrum remains unchanged in its oxime. It possesses provitamin A activity approximately one half that of β-carotene [33]

(XXXIV.) [chemical structure diagram: O: ·CH:ip:ip:pi:pi:CH·]
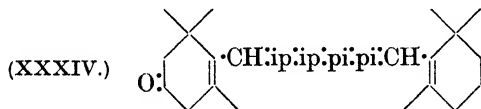
and the constitution (XXXIV), accommodating one unmodified β-ionone ring, has been suggested. Although the absorption spectrum of aphanin is similar to those of γ-carotene and rubixanthin, no *iso*propylidene group could be detected in the molecule. It is assumed, therefore, that the presence of the carbonyl group, although not in direct conjugation, modifies the β-carotene chromophore. Reduction with aluminium *iso*propoxide was attempted, but no cryptoxanthin could be isolated from the complex product, which did, however, exhibit the expected light absorption. Aphanicin, also epiphasic, resembles aphanin in many of its properties and since its provitamin A activity is about one quarter that of β-carotene it is suggested, on this basis alone, that it possesses the unusual "dicarotenoid" formula, $C_{80}H_{108}O_3$, including one unsubstituted β-ionone

[78] J. Tischer, *Z. physiol. Chem.*, 1938, **251**, 109; 1939, **260**, 257.

ring.   There would appear to be little justification for the employ-ment of growth-promoting tests in order to determine molecular weight.   Flavacin, a third epiphasic pigment, exhibits absorption maxima intermediate between those of violaxanthin and azafrin and is probably a hydrocarbon, and the hypophasic aphanizophyll, containing both hydroxyl and carbonyl groups, resembles lycopene in its light absorption properties.

The tetraketone " euglenarhodone," isolated   by J. Tischer [79] from the red euglena (*Euglena heliorubescens*) and later, as labile esters, from the red spores of *Hæmatococcus pluvialis*,[80] has been shown to be identical with astacene,[81] occurring in the spores as astaxanthin esters (*q.v.*).   It is somewhat remarkable that this pig-ment, hitherto considered to be a characteristic animal carotenoid, should occur in a green alga.   In addition the euglena contains β-carotene and esterified lutein and zeaxanthin, and the spores of the second alga yield the same pigments and also the new epiphasic hæmatoxanthin (abs. max. in carbon disulphide, 5150 A.).

In a recent publication [48] H. Kylin has collated his data on the carotenoids of the algæ, these results being based entirely on chromatographic and spectroscopic observations.   In general the results described, frequently from an examination of different algæ, are in accord with those of Carter, Heilbron, and Lythgoe, but Kylin considers that the occurrence of zeaxanthin in the dead Phæophyceæ is to be attributed, not to the post-mortem transformation of fuco-xanthin as was originally suggested by I. M. Heilbron and R. F. Phipers,[73] but to the destruction of the latter pigment, which renders possible the isolation of the small quantity of zeaxanthin originally present in the alga.   H. H. Strain [82] has observed a similar behaviour in yellowing leaves, which he attributes to the great stability of zeaxanthin towards acids and oxygen.

It has been concluded on spectrographic evidence [83] that caro-tenoids occur in the plastids of plants as a protein–pigment complex, the change in absorption spectrum on denaturation of the protein by heat being well illustrated with the fucoxanthin of brown algæ. The colour change observed in this way or by solvent treatment is presumably analogous, although not so striking in contrast, to the behaviour of the chromoprotein of the Crustaceæ on similar treatment.

Bacterial Carotenoids.—Numerous studies on the carotenoids of

[79] *Z. physiol. Chem.*, 1936, **239**, 257; 1939, **259**, 163.

[80] *Idem, ibid.*, 1937, **250**, 147; 1938, **252**, 225.

[81] R. Kuhn, J. Stene, and N. A. Sörensen, *Ber.*, 1939, **72**, 1688.

[82] " Leaf Xanthophylls."   Carnegie Institute of Washington Publication No. 490, 1938, 92.

[83] W. Menke, *Naturwiss.*, 1940, **28**, 31.

bacteria have been made,[84] but divergencies between the findings of different workers are frequent, doubtless partly owing to the difficulty of obtaining identical strains.

From the acid-fast lepra bacteria, *Mycobacterium phlei*, a hydrocarbon leprotene, $C_{40}H_{54}$, has been isolated along with some α- and γ-carotene and azafrin. It is similar to β-carotene in its light absorption and provitamin A activity but differs in its crystalline form and higher melting point.[85] The absence of xanthophylls from this and other bacteria is in agreement with a similar observation on the fungi (*q.v.*).[86]

The constitution of the carotenoid pigment, rhodoviolascin, $C_{42}H_{60}O_2$, isolated by Karrer and his collaborators from both *Rhodovibrio* and *Thiocystis* bacteria presents several points of interest.[87] This substance is remarkable in that, not only does it contain two methoxyl groups, thus accounting for its epiphasic nature, but it possesses thirteen ethylenic linkages which, from its light absorption at particularly long wave-lengths, must all be conjugated. Identification of bixin dialdehyde amongst the several products of permanganate degradation provides evidence for the " middle portion " of the molecule and the recognition of a hypophasic higher dialdehyde containing eleven conjugated double bonds

(XXXV.)   MeO·CH:ip:ip:pi:pi:CH·OMe
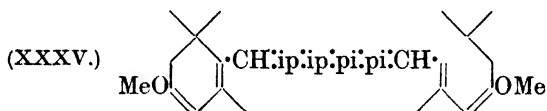
and no methoxyl groups suggests (XXXV) as a probable constitution for the pigment. The close similarity in absorption spectrum between rhodoviolascin and spirilloxanthin from *Spirillum rubrum* bacteria [88] may presage a chemical relationship between these two carotenoids.

Other pigments accompanying rhodoviolascin in the purple bacteria have not been available in sufficient quantity for the determination of conclusive constitutional data, but rhodopurpurin exhibits similar absorption maxima to, and may be identical with, lycopene. The epiphasic rhodopin, $C_{40}H_{58}O$, contains twelve

[84] For summaries, see E. Lederer, *Bull. Soc. Chim. biol.*, 1938, **20**, 611; P. Karrer and U. Solmssen, *Helv. Chim. Acta*, 1935, **18**, 1306.

[85] C. Grundmann and Y. Takeda, *Naturwiss.*, 1937, **25**, 27; Y. Takeda and T. Ohta, *Z. physiol. Chem.*, 1939, **258**, 6; **262**, 168; 1940, **265**, 233.

[86] See, however, M. A. Ingraham and H. Steenbock, *Biochem. J.*, 1935, **29**, 2553.

[87] P. Karrer and U. Solmssen, *Helv. Chim. Acta*, 1935, **18**, 1306; 1936, **19**, 3, 1019; P. Karrer, U. Solmssen, and H. Koenig, *ibid.*, 1938, **21**, 454; P. Karrer and H. Koenig, *ibid.*, 1940, **23**, 460.

[88] C. B. van Niel and J. H. C. Smith, *Arch. Microbiol.*, 1935, **6**, 219.

double bonds and, like the similarly epiphasic rhodovibrin, $C_{40}H_{58}O_2$, is also somewhat analogous to lycopene in its light absorption. β-Carotene is occasionally to be found in small quantities in the carotenoid mixture.

Carotenoids of the Fungi.—R. Emerson and D. L. Fox [89] have observed that the orange colour of the male gametes in the sexual phase of the aquatic fungus *Allomyces* is due to γ-carotene. Not even traces of xanthophylls could be detected and E. Lederer,[50] describing an examination of the carotenoid pigments of the cryptogams, also remarks on the absence of hypophasic xanthophylls from the lower fungi and suggests that it might be correlated with the inability of these organisms to synthesise chlorophyll. Epiphasic xanthophylls, such as torulene (abs. max. in carbon disulphide, 5660, 5220, 4910 and 4610 A.), occur in the lower fungi, and are reminiscent of the xanthophyll ethers from the purple bacteria. Few of the higher fungi are rich in carotenoid pigments; *Cantharellus cibarius*, however, is an exception.[90]

General.—An addition product of carotene with five molecules of maleic anhydride has been described.[91] It has been shown [92] that the bleaching of colloidal aqueous solutions of α- and β-carotenes is an oxidative process, accelerated with increasing light intensity. This light sensitivity of carotenoids is markedly dependent on the degree of dispersion of the colloid and is affected also by the presence of other substances, such as ascorbic acid and lecithin, which stabilise the solutions. Other workers [93] have examined the preparation and physicochemical properties of these colloidal solutions.

In general γ-carotene forms only a very small proportion of the total carotene of plants. In addition to the *Allomyces* already mentioned, however, the marsh dodder (*Cuscuta salina*) is a rich source of this hydrocarbon.[94]

A new xanthophyll, petaloxanthin, $C_{40}H_{58(56)}O_3$, has been isolated from the mature pumpkin flowers (*Curcubita pepo*).[95] It is differentiated from antheraxanthin[96] only by its facile separation by chromatographic methods from admixture with the latter.

No lutein could be found in the pondweed *Elodea canadensis*, its

[89] *Proc. Roy. Soc.*, 1940, B, **128**, 275.

[90] H. Willstaedt, *Svensk Kem. Tidskr.*, 1937, **49**, 318.

[91] J. Nakamiya, *Bull. Inst. Phys. Chem. Res. Tokyo*, 1936, **15**, 286.

[92] P. Karrer and W. Straus, *Helv. Chim. Acta*, 1938, **21**, 1624.

[93] F. A. Rachevskiï and G. V. Troitskiï, *Colloid J.*, *U.S.S.R.*, 1937, **3**, 469; S. D. Balakhovskiï and F. A. Rachevskiï, *Bull. Biol. Méd. exptl. U.R.S.S.*, 1938, **5**, 519.

[94] G. Mackinney, *J. Biol. Chem.*, 1935, **112**, 421.

[95] L. Zechmeister, T. Béres, and E. Ujhelyi, *Ber.*, 1936, **69**, 573.

[96] P. Karrer and A. Oswald, *Helv. Chim. Acta*, 1935, **18**, 1303.

place being taken by a new xanthophyll, eloxanthin,[97] isomeric with flavoxanthin. Again in the furze (*Ulex galli* and *europæus*) lutein is absent,[98] the xanthophylls consisting of violaxanthin, taraxanthin, and a pigment very closely related to lutein but melting some 10° higher. The flowers of the related *Genista tridentata*, on the other hand, contain only lutein and β-carotene.[99] From *Gazania rigens* a xanthophyll, gazaniaxanthin, $C_{40}H_{54(56)}O$, simulating rubixanthin in its physical and chemical properties, has been isolated.[100] Eschscholtzxanthin, $C_{40}H_{54 \pm 2}O_2$, from the petals of the Californian poppy (*Eschscholtzia californica*), is more unstable to oxygen than the common carotenoids. Although its absorption maxima proximate to those of lycopene, comparisons of the molecular extinction coefficients make its identity with lycoxanthophyll improbable.[101]

Analogous to the conversion of β-carotene into β-carotenone, physalien (zeaxanthin dipalmitate) has been oxidised to the tetraketone, physalienone.[102] Attempts to oxidise the diacetate were unsuccessful. Reinvestigation of the hydrogenation of violaxanthin gives figures corresponding to ten double bonds, which is in better agreement with the observed absorption spectrum.[103]

Animal Carotenoids.

This aspect of carotenoid chemistry has been treated comprehensively in a monograph by L. Zechmeister.[104] Mammalian carotenoids are invariably of alimentary origin,[105] but in birds and fish (in the feathers and skin respectively) there appear carotenoids, to some extent characteristic of the species, which are in all probability transformation products of the dietary pigments.[106] It should be noted that these specific animal carotenoids (*e.g.*, astacene), which tend to predominate in the invertebrates, are all xanthophylls and are frequently ketonic in nature.

Astacene and Astaxanthin.—Astacene, the characteristic pigment of the Crustaceæ, has been isolated from or detected in many invertebrates and also in some of the lower vertebrates ; [107] its constitution

[97] D. Hey, *Biochem. J.*, 1937, **31,** 532.

[98] K. Schön, *ibid.*, 1936, **30,** 1960.

[99] K. Schön and B. Mesquita, *ibid.*, p. 1966.

[100] K. Schön, *ibid.*, 1938, **32,** 1566 ; *Ann. Reports*, 1938, **35,** 368.

[101] H. H. Strain, *J. Biol. Chem.*, 1938, **123,** 425 ; *Ann. Reports*, 1938, **35,** 369.

[102] P. Karrer and W. Gugelmann, *Helv. Chim. Acta*, 1937, **20,** 405.

[103] P. Karrer and U. Solmssen, *ibid.*, 1936, **19,** 1024.

[104] *Ergebn. Physiol.*, 1937, **39,** 117.

[105] L. Zechmeister and P. Tuzson, *Z. physiol. Chem.*, 1934, **225,** 189.

[106] H. Brockmann and O. Völker, *ibid.*, 1934, **224,** 193.

[107] *Ann. Reports*, 1935, **32,** 300 ; *inter alia*, E. Lederer, *Bull. Soc. Chim. biol.*, 1938, **20,** 554, 567 ; N. A. Sörensen, *Kgl. Norske Videnskab Selskabs Skrifter*, 1936, No. 1 ; C. Manunta, *Helv. Chim. Acta*, 1939, **22,** 1154.

is well established but some doubt has hitherto existed as to the state of combination in which it occurs in Nature. R. Kuhn and N. A. Sörensen [108] have been able to demonstrate that the so-called red "ovo-ester" of astacene,[109] which is formed when the green chromoprotein of lobster eggs is heated or treated with solvents, is actually a xanthophyll, $C_{40}H_{52}O_4$, designated astaxanthin. The "ovo-ester" is converted into astacene, $C_{40}H_{48}O_4$, in alkaline solution, not by hydrolysis, but by an oxidation in which two moles of oxygen are smoothly taken up. Zerewitinoff determinations on

$$C_{40}H_{52}O_4 + 2O_2 \longrightarrow C_{40}H_{48}O_4 + 2H_2O_2$$
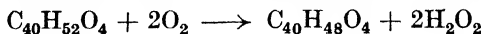
astaxanthin indicate only two active hydrogen atoms, and its diacetate fails to yield any methane, and since the xanthophyll does not enolise readily, it is suggested that its constitution may be represented by the double α-ketol formula (XXXVI). Autoxidation of such α-ketol groupings in alkaline media is well known. With alkali a deep blue potassium salt (XXXVII) is obtained, from
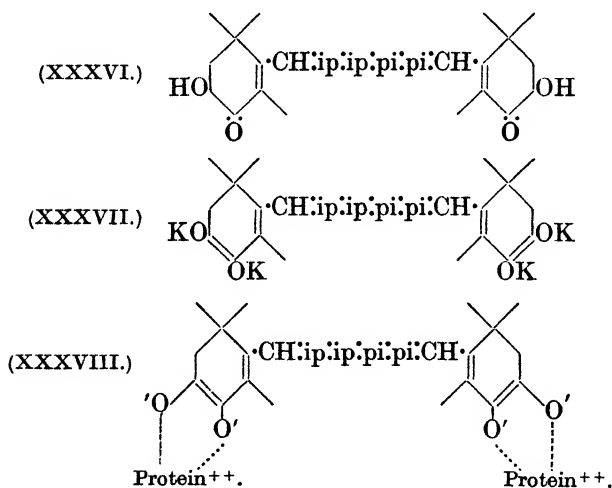
which astaxanthin can be recovered on acidification, but on admitting oxygen the colour of the solution changes immediately to red owing to the formation of astacene. Representation of the greenish-blue chromoprotein, ovoverdin, by a structure (XXXVIII), analogous to that of the potassium salt of astaxanthin, appears to explain the remarkable colour of the former, its insensitivity towards oxygen being attributed to the firm "anchoring" of the protein to the pigment. Ovoverdin has been purified by fractional chromato-

[108] Ber., 1938, 71, 1879; Angew. Chem., 1938, 51, 465.
[109] P. Karrer and H. Hübner, Helv. Chim. Acta, 1936, 19, 479.

graphic adsorption on alumina and elution with ammonium sulphate solution, and by determining the astacene : protein ratio in the purified material and assuming that the chromoprotein consists of one molecule each of astaxanthin and protein, a molecular weight of 144,000 is arrived at for the chromoprotein.

As a direct result of this work it appears improbable that astacene or astacene esters occur as such in nature, the astacene being an artefact produced by oxidation during either hydrolysis or putre-faction. R. Kuhn, J. Stene, and N. A. Sörensen [81] have surveyed a number of sources of astacene, and in each case the presence of astaxanthin, free, esterified or as a chromoprotein, has been established. It has been isolated from the retina of the hen and from fish liver (*Regalecus glesne*). The red hypodermis of the lobster contains astaxanthin esters, the colour of boiled lobster is due to astaxanthin, and it is the main pigment of trout flesh.[110]

E. Lederer [111] has described an examination of the skin pigments of six varieties of fish. Three of these contained " astacene esters," yielding astacene on hydrolysis, and the remainder contained a pigment resembling taraxanthin.[112] Astacene has also been isolated from two ascidians, and the crustacean *Calanus finmarchicus* gives a very high yield of this pigment.[113]

Other Animal Carotenoids.—Two new xanthophylls have been found in invertebrates.[113] Cynthiaxanthin, isolated from the ascidian *Halocynthia papillosa,* along with astacene, and character-ised by absorption maxima at 5170, 4830, and 4510 A. (carbon disul-phide), is similar to zeaxanthin. Pectenoxanthin, $C_{40}H_{54}O_3$, from the genital organs of the mollusc *Pecten maximus*, exhibits absorption maxima at similar wave-lengths. It contains eleven conjugated ethenoid linkages and probably two hydroxyl groups and, as would be expected from the oxygen content, has no provitamin A pro-perties. These two new pigments were isolated during an examin-ation of the carotenoid content of a number of invertebrates and Lederer remarks on the absence in the marine animals studied of any typical plant xanthophylls, in spite of the presence of these in the algæ on which the animals feed.

Echinenone [114] is similar in some respects to myxoxanthin,[77] and, like the latter, is biologically active.[32] It is the first animal carotenoid found to possess provitamin A properties. The red

[110] N. A. Sörensen and J. Stene, *Kgl. Norske Videnskab Selskabs Skrifter*, 1939, No. 9.

[111] *Bull. Soc. Chim. biol.*, 1938, **20,** 554.

[112] See also F. B. Sumner and D. L. Fox, *J. Exp. Zoology*, 1933, **60,** 263.

[113] E. Lederer, *Bull. Soc. Chim. biol.*, 1938, **20,** 567.

[114] E. Lederer, *Compt. rend.*, 1935, **201,** 300; *Bull. Soc. Chim. biol.*, 1938, **20,** 567; *Ann. Reports*, 1935, **32,** 304.

sponge, *Hymeniacidon sanguineum*, Grant., contains echinenone and γ-carotene.[115]

The carotenoids of the lower vertebrates have been extensively studied by E. Lönnberg,[116] but since in general the pigments were not separated chromatographically and never obtained crystalline, the survey loses much of its value.

<div align="right">E. R. H. J.</div>

6. MACROCYCLIC AND RELATED PIGMENTS.

General.

Since the last Report [1] on this subject, much work has been done on materials intermediate between phthalocyanine [2] and the porphyrins. A modified formula has been proposed for chlorophyll,[3] and progress made towards its ultimate synthesis. In view of notable advances in the study of bilirubinoids a section has been devoted to linear pigments.

J. M. Robertson and (Miss) I. Woodward [4] suggested that the smaller departure from tetragonal symmetry in the nickel phthalocyanine molecule as compared with the free pigment might be due to the replacement of two N–H–N bridges (I) by the four Ni–N covalencies which are identical if the double bonds are mobile. They now show [5] that the platinum complex exhibits a still smaller deviation from symmetry (and a change in the packing of the molecules). The infra-red absorption of porphyrins and dipyrrylmethenes is suggestively consistent with, but does not establish, the presence of N–H–N bridges.[6]
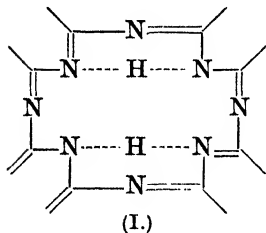
(I.)

If the double bonds are fixed, porphyrins should exist in two isomeric forms defined by the relative positions of the imino-hydrogen atoms or alternatively of the pyrrolenine nuclei. P. Rothemund [7] has isolated two products in many cases in his

[115] P. J. Drumm and W. F. O'Connor, *Nature*, 1940, **145**, 425.

[116] *Inter alia, Archiv. Zool.*, 1939, **31**, *A*, No. 1; 1938, **30**, *A*, No. 6; 1937, **29**, *B*, No. 4; 1936, **28**, *A*, No. 15.

[1] *Ann. Reports*, 1937, **34**, 369.

[2] Summarising lecture on phthalocyanines by R. P. Linstead, *Ber.*, 1939, **72**, *A*, 93.

[3] Chlorophyll and its derivatives are exhaustively treated by H. Fischer and H. Orth : " Die Chemie des Pyrrols," Vol. II, Part 2 (1940).

[4] *J.*, 1937, 219.   [5] *J.*, 1940, 36.

[6] C. S. Vestling and J. R. Downing, *J. Amer. Chem. Soc.*, 1939, **61**, 3511.

[7] *Ibid.*, 1936, **58**, 625; 1939, **61**, 2912.

syntheses of porphyrins, and regards them as isomerides of this kind. The distinction persists in the metallic complexes, but the pub-

4 Pyrrole
+   ⟶
4 RCHO
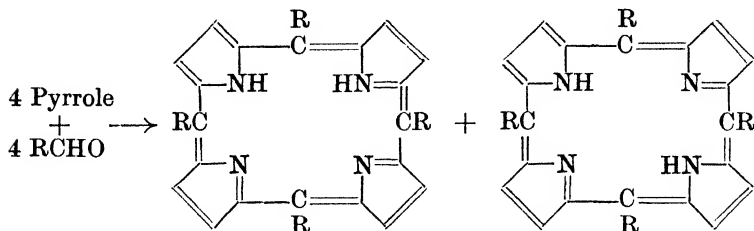
lished experimental data are insufficient to establish isomerism. By heating a substance formed in the hydrogenation of o-cyano-acetophenone, J. H. Helberger and A. von Rebay [8] obtained an " isotetrabenzoporphin," which may be a similar isomeride of the known tetrabenzporphin, although the possibility of its containing additional hydrogen is not excluded.

A. Stern,[1] who regarded the pyrrolenine ring as the fundamental chromophore of the porphyrin molecule, was led by a study of the effect of carbonyl substitution on the absorption spectra to the conclusion that the pyrrolenine nuclei occupy opposite positions, with fixation of the double bonds. F. Haurowitz [9] attributes the four bands in the visible region which are totally altered by salt-formation, to the nitrogenous basic system, and the unaffected band near 4000 A. to the conjugated outer ring. Stressing the aromatic behaviour of porphyrins and the absence of localised double bonds in phthalocyanine as shown by the X-ray analyses, he regards porphin as a resonance hybrid of the structures typified by (II), in which the nitrogen atom of ring IV carries an electron sextet; one hydrogen atom is considered to bridge the nitrogen atoms of rings I and IV and the other those of rings II and III. It may well be objected that the 4000 A. band persists in the 7 : 8-dihydroporphins of the chlorophyll series [10] in which the conjugation of the outer ring of (II) would be broken.

The aromatic character of the porphin ring suggests that the outer benzene nuclei of phthalocyanine should exhibit the ready substitution of diphenyl rather than the reluctance of phthalic acid derivatives. Halogenation of these rings, preferentially in the 4- and 5-positions, has been achieved without difficulty, and is preceded by addition.[11]

[8] *Annalen*, 1939, **539**, 187.   [9] *Ber.*, 1938, **71**, 1404.

[10] A. Stern, *Z. physikal. Chem.*, 1938, *A*, **182**, 186.

[11] P. A. Barrett, E. F. Bradbrook, C. E. Dent, and R. P. Linstead, *J.*, 1939, 1820.

(Mrs.) K. Lonsdale [12] has published further details of her study of the magnetic anisotropy of phthalocyanine.

(II.)

(III.)
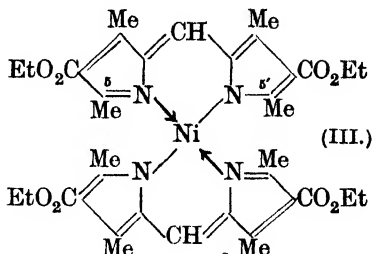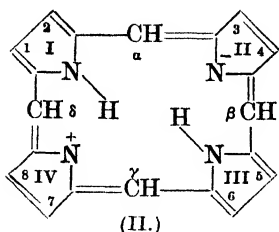
Metallic Complexes.—H. Senff and W. Klemm [13] infer from the magnetic susceptibilities of the phthalocyanine complexes of bivalent manganese, iron, cobalt, and nickel, that their predominantly covalent character increases in that order; in the pyridine and quinoline adducts of the ferrous compound the metal is 6-covalent. The nickel complex of protoporphyrin is covalent, but of the iron derivatives only the ammines of the ferrous complex.[14]

It is clear that in these substances the cyclic system imposes a planar configuration on the valencies of the metallic atom. Dipyrrylmethenes form similar complexes in which two molecules of methene replace one of porphin, and the molecular dimensions are such that if both methenes are substituted in positions 5 and 5′ the planar configuration cannot be maintained owing to overlapping of these substituents. The nickel compound (III) of this type is paramagnetic, corresponding to a largely ionic linking of the nickel atom in keeping with the non-planar arrangement of its valencies.[15]

W. M. Clark, J. F. Taylor, T. H. Davies, C. S. Vestling, and (Miss) M. E. Perkins [16] have published the preliminary results of a general potentiometric and spectrophotometric study of oxidation–reduction equilibria, ionisation, and dissociation in metallic derivatives of porphyrins and their compounds with organic bases.

The following new metallic derivatives of phthalocyanine (PcH_2) have been prepared [17] by known methods : $PcLi_2$; $PcHLi$; $PcSbCl$; palladium chlorophthalocyanine. The very soluble dilithium compound cannot be methylated; it yields by double

[12] *J.*, 1938, 364.   [13] *J. pr. Chem.*, 1939, **154**, 73.

[14] L. Pauling and C. D. Coryell, *Proc. Nat. Acad. Sci.*, 1936, **22**, 159.

[15] C. R. Porter, *J.*, 1938, 368; D. P. Mellor and W. H. Lockwood, *Nature*, 1940, **145**, 862; *Ann. Reports*, 1938, **35**, 164.

[16] *J. Biol. Chem.*, 1940, **135**, 543, 569, 597, 623, 643.

[17] P. A. Barrett, D. A. Frye, and R. P. Linstead, *J.*, 1938, 1157.

decomposition the silver (PcAg^{II} or PcHAg^{I}) and mercury (PcHg) complexes, which last is also [18] obtained by heating phthalonitrile with diphenylmercury. Fusion of phthalonitrile with metallic antimony affords an unstable substance of the anomalous composition PcSb$_2$. The soluble silver and chloroantimony derivatives can be sublimed and appear to be covalent in contrast with the mercury compound. Organic bases combine with the ferrous complex,[13, 17] from which the " hæmin " PcFeCl has been obtained pure by the action of air and hydrochloric acid. J. S. Anderson, E. F. Bradbrook, A. H. Cook, and R. P. Linstead [19] have determined the absorption spectra of phthalocyanine, many of its metallic derivatives, and some related compounds. A nearly constant frequency difference of 1585 cm.$^{-1}$ is found in the spectra of all these materials, and is compared with the 1560 cm.$^{-1}$ term [20] in the spectra of porphyrins.

The decomposition of hydrogen peroxide is strongly catalysed by the iron complexes of phthalocyanine or octaphenyltetrazaporphin, but not by the free pigments or their complexes with other metals.[21] Charcoal as a carrier promotes the reaction and cyanides are markedly inhibitory. Similar observations have been made on the catalysis of the oxidation of " luminol " with hydrogen peroxide.[22, 23] The magnesium complexes of phthalocyanine and of porphyrins in general, and also chlorophylls a and b, cause a brilliant red luminescence in hot tetrahydronaphthalene, which depends on the conversion of " tetralin peroxide " ($C_{10}H_{11}O_2H$) into α-tetralone and is accompanied by oxidation of the pigment.[22, 24] Complexes of phthalocyanine and its allies with iron, but not with other metals, promote the atmospheric oxidation of benzaldehyde, polyhydric phenols, and many other substances, with simultaneous decolorisation of the pigment; the analogy to biological oxidations is emphasised.[25] Tetralin is similarly oxidised to α-tetralone, and unsaturated hydrocarbons yield mainly αβ-unsaturated ketones;[26] it is held that the catalyst acts by promoting this decomposition, as against the reversible dissociation, of a peroxide formed by atmospheric oxidation.

Tetrabenzazaporphins.—The complete series of compounds has

[18] I. G. Farbenindustrie, *B.*, 1938, 765.
[19] *J.*, 1938, 1151.
[20] H. Hellström, *Arkiv Kemi Min. Geol.*, 1936, **12**, *B*, no. 13.
[21] A. H. Cook, *J.*, 1938, 1761.   [22] *Idem, ibid.*, p. 1845.
[23] H. Thielert and P. Pfeiffer, *Ber.*, 1938, **71**, 1399.
[24] J. H. Helberger and D. B. Hevér, *Ber.*, 1939, **72**, 11.
[25] A. H. Cook, *J.*, 1938, 1768.
[26] *Idem, ibid.*, p. 1774; C. Paquot, *Compt. rend.*, 1939, **209**, 171; see also B. Tamamushi and S. Tohmatsu, *Bull. Chem. Soc. Japan*, 1940, **15**, 223.

been described, from tetrabenzporphin (IV), with its four *iso*-indole nuclei linked by methin groups, to tetrabenztetrazaporphin
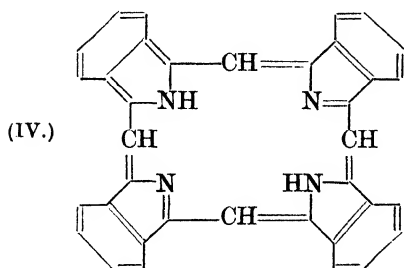
(phthalocyanine) in which all four methin groups are replaced by nitrogen atoms. The preparation of phthalocyanine from *o*-cyano-benzamide probably proceeds *via* iminophthalimidine (V; $R_1R_2 =$ NH), and in other syntheses from *o*-substituted benzonitriles the intermediate production of an *iso*indole or its metallic derivative can be postulated with greater or less plausibility, whereupon addition or condensation reactions of known types can lead to the final pigment.[8, 27] Much work has been done on the preparation of pigments from materials * containing the *iso*indole ring already closed. *iso*Indolinones (phthalimidines) (V; $R_1R_2 =$ Me, H;[28] $CH_2 \cdot CO_2H$, H;[27] CH_2;[29] $CH \cdot CO_2H$ [29, 30]) give mainly tetrabenz-porphin when fused with metals or their oxides or acetates; addition of phthalonitrile leads to the formation of azaporphins, usually inhomogeneous. While the imine (V; $R_1R_2 =$ NH) yields phthalo-cyanine, the substance (VI) gives mainly the monoaza-pigment,
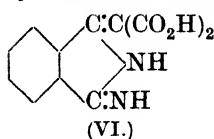
and the di- or tri-aza in presence of phthalo-nitrile.[27] In these syntheses the use of zinc or of metallic acetates favours the production of methin links; indeed the acetate radical may itself provide the methin carbon atom as in the formation of tetrabenzporphin from phthalimide or phthalimidine and zinc acetate.[30] Ethyl- and ethylidene-phthalimidines yield tetrabenzporphin with loss of a methyl group, recalling the lability of the same radical attached to a methin bridge in phylloporphyrin.[30] Tetrabenztriazaporphin is produced in tolerable yield by heating in

[27] P. A. Barrett, R. P. Linstead, F. G. Rundall, and G. A. P. Tuey, *J.*, 1940, 1079.

[28] J. H. Helberger, A. von Rebay, and D. B. Hevér, *Annalen*, 1938, **533**, 197.

[29] C. E. Dent, *J.*, 1938, 1.

[30] J. H. Helberger and D. B. Hevér, *Annalen*, 1938, **536**, 173.

* Compare p. 367.

a high-boiling solvent the product of interaction of phthalonitrile and methylmagnesium iodide or methyl-lithium; *n*-butyl-lithium gives the same product.   If excess of the organometallic reagent is used, a tetrabenzmonoazaporphin is obtained, and other conditions lead to a simple *iso*indole derivative.[27, 31]

The individuality of the absorption spectra shows that the products are homogeneous and not isomorphous mixtures, except in the case of the diaza-compound, which could also be a mixture of position isomerides.   These conclusions are confirmed by oxidation of the pigments with ceric sulphate, which yields four molecules of phthalimide with four of carbon dioxide and/or ammonia, the calculated amount of oxidising agent being consumed.[27, 31] The table [27] below illustrates the gradation in properties in this series.   Preliminary X-ray studies [32] show a close correspondence in cell-dimensions between phthalocyanine and tetrabenztriazaporphin, and between the monoaza-compound and tetrabenzporphin, the considerable difference between former and latter pairs indicating a change in the packing of the molecules.

No. of bridge nitrogen atoms.	4.	3.	1.	0.
Preparative source.	Phthalonitrile and metals.	Phthalonitrile and Grignard reagent.[31]	(VI) and zinc.[27]	(V; $R_1R_2 =$ $CH_2 \cdot CO_2H,H$) and zinc.[27]
Ease of formation	$\longleftarrow$———————— Increases ————————			
Stability to oxidation	———————— Increases ————————$\longrightarrow$			
Solubility in organic media	———————— Increases ————————$\longrightarrow$			
Ease of sublimation	$\longleftarrow$———————— Increases ————————			
λ of main bands in red	$\longleftarrow$———————— Increases ————————			
Intensity of bands in violet	———————— Increases greatly ————————$\longrightarrow$			
Stability of metal complexes	$\longleftarrow$———————— Increases ————————			
Basicity	———————— Increases ————————$\longrightarrow$			

Simple   Azaporphins.—When   dipyrrylmethenes   of   the   type (VII) are heated with sodium hydroxide and quinoline, they afford monoazaporphins in modest but improved yield, with loss of the carbon atom of one bromomethyl group.[33] By pyrolysis, 2-aldehydopyrrole-5-urethanes give diazaporphins with similar loss

[31] P. A. Barrett, R. P. Linstead, and G. A. P. Tuey, *J.*, 1939, 1809.

[32] J. M. Robertson, *J.*, 1939, 1811; (Miss) I. Woodward, *J.*, 1940, 601.

[33] F. Endermann and H. Fischer, *Annalen*, 1939, **538**, 172.

of carbon, and a mixture of tetrazaætioporphyrins is obtained from 2 : 5-dicarbimido-3-methyl-4-ethylpyrrole.

(VII.)
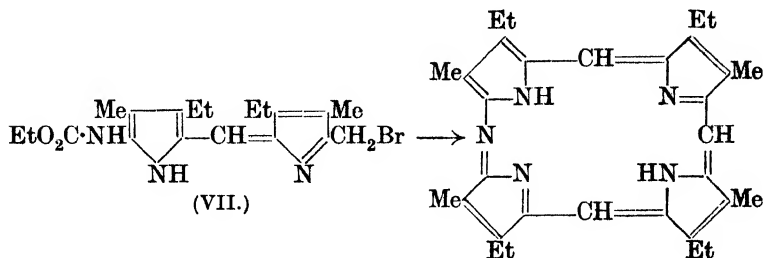
Chlorophyll.

The Extra Hydrogen Atoms.—A systematic study [34] of the oxidation products of chlorophyll derivatives leads to the conclusion that the " extra hydrogens " should be placed on the 7- and 8-carbon atoms of ring IV (I) and not in positions 5 and 6.[35] Thus, whereas unreduced porphyrins from chlorophyll yield hæmatic acid (II) in quantity (from ring IV), none is obtained from phorbides and chlorins, which yield instead an undefined, *strongly lævorotatory* acid fraction. Moreover, on the assumption that pyrroline rings cannot yield maleinimides (established for monocyclic Δ^3-pyrrolines),[34] the extra hydrogens cannot be in ring II, since chlorophyll derivatives regularly yield methylethylmaleinimide, or in ring I, since derivatives with the vinyl group reduced afford twice as much. Finally the production of citraconimide from phyllochlorin (III) rules out ring III. Chlorophyll *a* is therefore formulated as (I), subject to doubtfully significant discussion of the precise arrangement of double bonds.

(I.)

(II).

(III.)
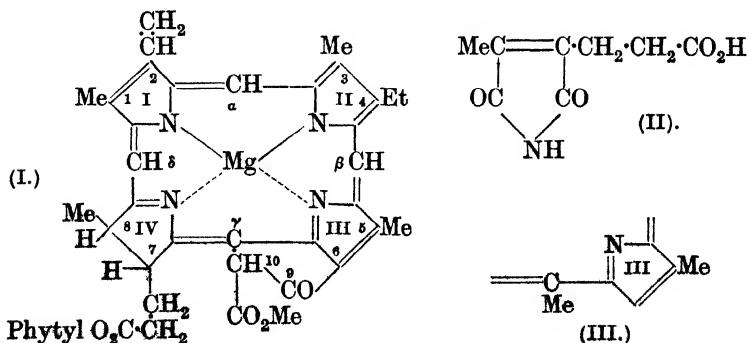
[34] H. Fischer and H. Wenderoth, *Annalen*, 1939, **537**, 170; see also ref. 1, p. 378.

[35] Formula (XI) of ref. 1.

Synthesis.—Removal of the magnesium atom and the phytyl group from chlorophyll a yields phæophorbide a, which is converted by hydriodic acid into the isomeric phæoporphyrin a_5 with loss of the extra hydrogens and compensating reduction of the vinyl group. The total synthesis of this porphyrin has now been completed. Phylloporphyrin [36] methyl ester (IV) * was oxidised with iodine and sodium acetate [37] to (V), which, *via* the cyanohydrin, afforded the methyl ester (VI) of *iso*chloroporphyrin e_4 ; [38] this had been converted by dichloromethyl ether–ferric chloride into (VII) and thence into phæoporphyrin a_5 (VIII). [1, 39]

$$\mathbf{P}\!\!<\!\!\begin{array}{l}\text{Et (2)}\\\text{H (6)}\\\text{Me }(\gamma)\end{array} \qquad \mathbf{P}\!\!<\!\!\begin{array}{l}\text{Et}\\\text{H}\\\text{CHO}\end{array} \qquad \mathbf{P}\!\!<\!\!\begin{array}{l}\text{Et}\\\text{H}\\\text{CH}_2\!\cdot\!\text{CO}_2\text{Me}\end{array}$$
$$\text{(IV.)} \qquad\qquad\qquad \text{(V.)} \qquad\qquad\qquad \text{(VI.)}$$

$$\text{(VII.)}\quad \mathbf{P}\!\!<\!\!\begin{array}{l}\text{Et}\\\text{CH}\cdot\text{OH}\\\text{CH}\cdot\text{CO}_2\text{Me}\end{array} \qquad\qquad \mathbf{P}\!\!<\!\!\begin{array}{l}\text{Et}\\\text{CO}\\\text{CH}\cdot\text{CO}_2\text{Me}\end{array}\quad\text{(VIII.)}$$
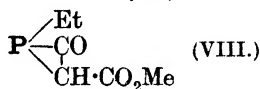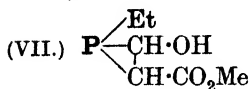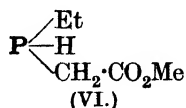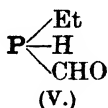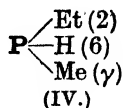
New partial syntheses of the homocyclic ring include the conversion of pyrroporphyrin (IX) into phylloerythrin (X), [39] of formyl-pyrroporphyrin (V) into 10-cyanodeoxophylloerythrin (XI), [40] and of meso*iso*chlorin e_4 (XII) into mesopyrophæophorbide a (XIII). [39] Since the last-named synthetic product has the correct rotation, it is unlikely that its formation involves the creation of a new asymmetric centre at C_6, as would be the case if the extra hydrogens were situated in the 5- and 6-positions.

$$\text{(IX.)}\quad \mathbf{P}\!\!<\!\!\begin{array}{l}\text{Et (2)}\\\text{H (6)}\\\text{H }(\gamma)\end{array} \longrightarrow \mathbf{P}\!\!<\!\!\begin{array}{l}\text{Et}\\\text{CO}\cdot\text{CH}_2\text{Cl}\\\text{H}\end{array} \xrightarrow[\text{acid fusion}]{\text{succinic}} \mathbf{P}\!\!<\!\!\begin{array}{l}\text{Et}\\\text{CO}\\\text{CH}_2\end{array}\quad\text{(X.)}$$

$$\text{(V)} \longrightarrow \mathbf{P}\!\!<\!\!\begin{array}{l}\text{Et}\\\text{H}\quad\text{CO}_2\text{Me}\\\text{CH}\!=\!\text{C}\cdot\text{CN}\end{array} \xrightarrow[\text{melt}]{\text{succinic}} \mathbf{P}\!\!<\!\!\begin{array}{l}\text{Et}\\\text{CN}\\\text{C}\cdot\text{CO}_2\text{Me}\\\text{CH}_2\end{array} \xrightarrow{\text{H}_2\text{SO}_4} \mathbf{P}\!\!<\!\!\begin{array}{l}\text{Et}\\\text{CH}\cdot\text{CN}\\\text{CH}_2\end{array}$$
$$\text{(XI.)}$$

$$\text{(XII.)}\quad \mathbf{H}_2\mathbf{P}\!\!<\!\!\begin{array}{l}\text{Et (2)}\\\text{H (6)}\\\text{CH}_2\!\cdot\!\text{CO}_2\text{H }(\gamma)\end{array} \xrightarrow{\text{H}_2\text{SO}_4} \mathbf{H}_2\mathbf{P}\!\!<\!\!\begin{array}{l}\text{Et}\\\text{CO}\\\text{CH}_2\end{array}\quad\text{(XIII.)}$$
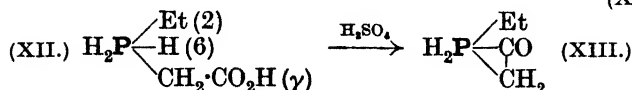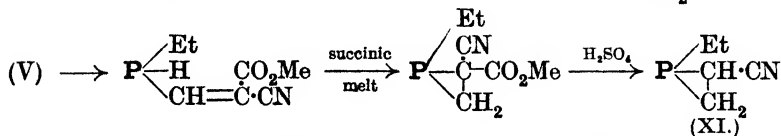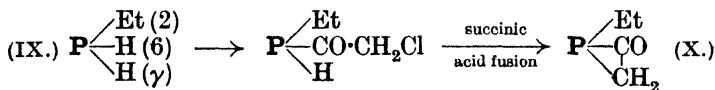
[36] Synthesis : H. Fischer and H. Helberger, *Annalen*, 1930, **480**, 235.
[37] H. Fischer and E. Stier, *ibid.*, 1939, **542**, 224.
[38] H. Fischer, E. Stier, and W. Kanngiesser, *ibid.*, 1940, **543**, 258.
[39] H. Fischer and O. Laubereau, *ibid.*, 1938, **535**, 17.
[40] H. Fischer and W. Kanngiesser, *ibid.*, 1940, **543**, 271.

* For brevity the porphin ring is represented by **P** and the dihydroporphin system by $\mathbf{H}_2\mathbf{P}$; unless otherwise indicated, the substituents are those of formula (I) apart from the magnesium atom and phytyl group.

Purpurins and Related Compounds.[41]—Atmospheric oxidation, often in propyl-alcoholic potash, of phæophorbide a, and analogously of other phorbides or of chlorins which can yield phorbides in presence of alkali,[42] affords an " unstable chlorin," characterised by its spectrum, but not crystallised, which is converted by diazomethane into the ester of purpurin 7.* Since purpurin 7, though it yields potassium oxalate on hydrolysis, does not react as a ketone, the formula (XV) † was considered as an alternative to (XIV), but (XV) is refuted by the preparation [43] of an analogous purpurin from 7 : 8-dihydroxychlorin e_6.† The " unstable chlorin " is formulated as the cyclic tautomer (XVI) of free purpurin 7. Oxidation of phæophorbide a in pyridine with oxygen or permanganate yielded the stable monomethyl ester (XVI), hydrolysable to the unstable chlorin and giving purpurin 7 trimethyl ester on esterification (Fischer–Speier or diazomethane).[42] Similar oxidation of chlorin e_6 gave an aldehyde,

$$
\begin{array}{ccc}
\text{H}_2\text{P}\!\!<\!\!\begin{array}{l}\text{CO}_2\text{Me (6)}\\ \text{CO·CO}_2\text{Me } (\gamma)\\ \text{H (7)}\\ [\text{CH}_2]_2\text{·CO}_2\text{Me (7)}\end{array} &
\text{H}_2\text{P}\!\!<\!\!\begin{array}{l}\text{CO}_2\text{Me}\\ \text{CH·CO}_2\text{Me}\\ \text{O}\\ [\text{CH}_2]_2\text{·CO}_2\text{Me}\end{array} &
\text{H}_2\text{P}\!\!<\!\!\begin{array}{l}\text{CO (6)}\\ \text{>O}\\ \text{C·CO}_2\text{H(Me) } (\gamma)\\ \text{OH}\end{array}\\
\text{(XIV.)} & \text{(XV.)} & \text{(XVI.)}
\end{array}
$$
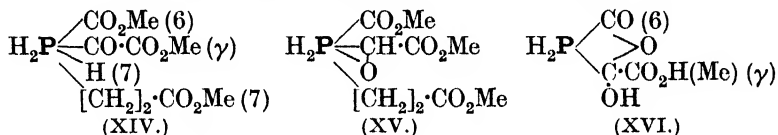
purpurin 5 (XVII), together with " rhodochlorin-γ-oxymethyl lactone " (XVIII). Purpurin 5 is best prepared [43] by treating with propyl-alcoholic potash the monomethyl ester-methylamide of chlorin e_6 obtained by the action of methylamine on phæophorbide a. These formulations are confirmed by earlier and more complete studies of similar transformations in the porphyrin series, and by conversion of (XVI) into the isomeric known phæoporphyrin a_7. Oxidation of purpurin 7,[42] or of bacteriomethylphæophorbide,[44]

$$
\text{H}_2\text{P}\!\!<\!\!\begin{array}{l}\text{CO}_2\text{H (6)}\\ \text{CH}_2\text{·CO}_2\text{H } (\gamma)\end{array} \longrightarrow \left[\text{H}_2\text{P}\!\!<\!\!\begin{array}{l}\text{CO}_2\text{H}\\ \text{CH(OH)·CO}_2\text{H}\end{array}\right] \longrightarrow \text{H}_2\text{P}\!\!<\!\!\begin{array}{l}\text{CO}\\ \text{>O}\\ \text{CH·OH}\end{array}
$$

$$
\downarrow \qquad\qquad \text{CH}_2\text{N}_2 \downarrow
$$

$$
\begin{array}{ccc}
\text{H}_2\text{P}\!\!<\!\!\begin{array}{l}\text{H (6)}\\ \text{CHO } (\gamma)\end{array} &
\text{H}_2\text{P}\!\!<\!\!\begin{array}{l}\text{CO}\\ \text{>O}\\ \text{CH}_2\end{array} &
\text{H}_2\text{P}\!\!<\!\!\begin{array}{l}\text{CO}_2\text{Me}\\ \text{CHO}\end{array}\\
\text{(XIX.)} & \text{(XVIII.)} & \text{(XVII.)}
\end{array}
$$
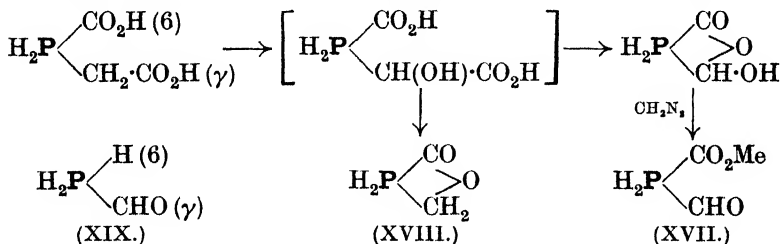
[41] See *Ann. Reports*, 1935, **32**, 385—389.

[42] H. Fischer and K. Kahr, *Annalen*, 1937, **531**, 209.

[43] H. Fischer and M. Conrad, *ibid.*, 1939, **538**, 143.

[44] H. Fischer, R. Lambrecht, and H. Mittenzwei, *Z. physiol. Chem.*, 1938, **253**, 1.

* Except in the case of purpurin 18, the numeral suffixes show the number of oxygen atoms in the molecule.

† The original formula and designation have been altered to accord with the new chlorophyll formula (I).

yields purpurin 9 (as XIV, but with CO_2H for vinyl in 2); γ-formyl-pyrrochlorin (XIX), from oxidation of *iso*chlorin e_4,[42] is regarded as purpurin 3. These purpurins, which have in common carbonyl substitution in γ, differ in general from chlorins in their dextro-rotation, visible colour, and modified absorption spectrum. Parallel transformations in the b series have been further studied,[43, 45] and the reaction has been extended to bacteriochlorophyll.[44]

When purpurin 5 is treated with methyl-alcoholic potash it yields first *iso*purpurin 5 (XX) and then strongly lævorotatory *neo*purpurin 4 (XXI); analogous γ-formyldihydroporphins, but not unreduced porphyrins, behave similarly, and purpurin 7 also yields an *iso*-purpurin.[46]

$$H_2P{\Big\langle}{\begin{matrix} CO_2Me\ (6) \\ CHO\ (\gamma) \\ CH_2 \cdot CH_2 \cdot CO_2Me\ (7) \end{matrix}} \longrightarrow H_2P{\Big\langle}{\begin{matrix} CO_2Me \\ CH \cdot OH \\ CH_2 \cdot CH \cdot CO_2Me \end{matrix}} \longrightarrow H_2P{\Big\langle}{\begin{matrix} CO_2Me \\ CH \\ CH_2 \cdot C \cdot CO_2Me \end{matrix}}$$

$$\text{(XX.)} \qquad\qquad \text{(XXI.)}$$
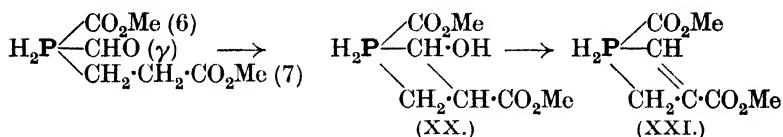
ψ-*Chlorin* p_6 *and Isomeric Rhodoporphyrin-γ-carboxylic Acid.*—It now [47] appears that these and related materials contain one carbon atom more than was supposed; the named substances are impure specimens of chlorin e_6 and chloroporphyrin e_6 respectively, and the puzzling isomerism does not exist.

Vinylporphyrins : Protochlorophyll.—While the familiar con-version of phorbides and chlorins into porphyrins by hydriodic acid involves simultaneous reduction of the vinyl group, controlled treatment with alkali or pyridine has led in a few cases to porphyrins with the vinyl radical unaltered. It is now found that this dehydro-genation can be effected by iron and formic acid.[48, 49] Thus methyl-phæophorbide a and chlorin e_6 trimethyl ester yield respectively 2-vinyl-2-desethylphæoporphyrin a_5 (loosely termed vinylphæo-porphyrin a_5) and vinylchloroporphyrin e_6. The same vinyl-phæoporphyrin is obtained when the protochlorophyll of the skins of gourd seeds is freed from magnesium by oxalic acid.[49, 50] Proto-chlorophyll and its derivatives are therefore unreduced porphyrins, as their spectra would suggest.[48] Further new vinylporphyrins

[45] H. Fischer and K. Bauer, *Annalen*, 1936, **523**, 235.
[46] H. Fischer and M. Strell, *ibid.*, 1939, **538**, 157; **540**, 232.
[47] H. Fischer, K. Kahr, M. Strell, H. Wenderoth, and H. Walther, *Annalen*, 1938, **534**, 292.
[48] K. Noack and W. Kiessling, *Z. physiol. Chem.*, 1929, **182**, 13; 1930, **193**, 97.
[49] H. Fischer, A. Oestreicher, and A. Albert, *Annalen*, 1939, **538**, 128.
[50] H. Fischer, H. Mittenzwei, and A. Oestreicher, *Z. physiol. Chem.*, 1939, **257**, IV.

are : vinylphylloerythrin;[49] vinylphylloporphyrin;[51] vinyl*iso*chloroporphyrin e_4;[52] 2-vinyl- and 2-vinyl-γ-formyl-pyrroporphyrin.[53]

Bacteriochlorophyll.[44]—The relationship of bacteriochlorophyll to chlorophyll has been clarified. The presence of a phytyl ester group is confirmed, and its hydrolysis by the highly specific [54] chlorophyllase shows that the rest of the molecule must be very similar to chlorophyllin. Since bacterio-methyl phæophorbide contains neither vinyl nor hydroxyethyl radicals, the conversion of bacteriochlorophyll derivatives into acetylporphyrins implies an acetyl group in the original substances. Analysis suggests that compounds of this series contain four hydrogen atoms more than the related porphyrins, and this is established by quantitative dehydrogenation of bacterio-methyl phæophorbide to " 2-acetylphæophorbide *a* " (identical with the by-product encountered in the extraction of bacteriophæophorbide), and of bacteriochlorin trimethyl ester to " 2-acetylchlorin e_6 trimethyl ester." The last-mentioned substance has been synthesised from and converted into chlorin e_6 by the transformations ·CH:CH$_2$ $\rightleftharpoons$ ·CH(OH)·CH$_3$ $\rightleftharpoons$ ·CO·CH$_3$ and, like the ester of chlorin e_6, regenerates the corresponding phæophorbide with methyl-alcoholic potash.[55] Owing to intense absorption, the optical activity of bacteriochlorophyll and its immediate derivatives cannot be observed, but the rotations of the dehydrogenation products can be roughly estimated and agree with those of the materials synthesised from chlorin e.[44] Bacteriochlorophyll is therefore an acetyldihydrochlorophyll a and is formulated as (XXII), the additional hydrogen atoms being assigned to
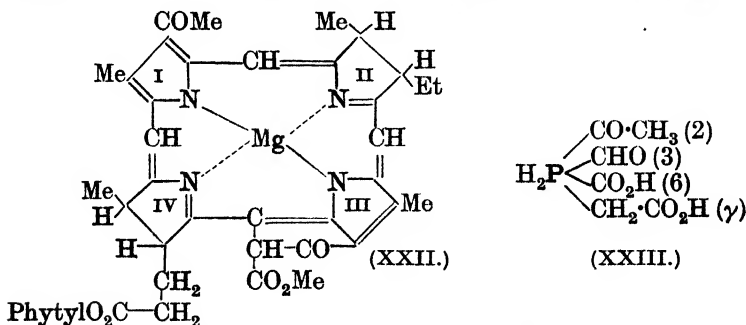
ring II, since oxidation of bacteriochlorin [34] gives no methylethylmaleinimide, but a dextrorotatory basic fraction, in addition to

[51] H. Fischer and S. F. MacDonald, *Annalen*, 1939, **540**, 211.

[52] H. Fischer and J. M. Ortiz-Velez, *ibid.*, p. 224.

[53] H. Fischer and M. Strell, *ibid.*, 1940, **543**, 143.

[54] H. Fischer and R. Lambrecht, *Z. physiol. Chem.*, 1938, **253**, 253.

[55] H. Fischer, W. Lautsch, and K. H. Lin, *Annalen*, 1938, **534**, 1.

a lævorotatory acid fraction as with chlorophyll derivatives. A. Stern and (Frl.) F. Pruckner [56] have measured the absorption of compounds of this series. There is no evidence of the natural occurrence of a bacteriochlorophyll b, but 2-acetylrhodin g_7 (XXIII) has been synthesised as the expected dehydrogenation product of a hypothetical bacteriorhodin.[49]

Miscellaneous.—The vinyl groups of phorbides and chlorins can be replaced by hydrogen by fusing the ferric complexes of the methyl esters with resorcinol.[57] Thus methylphæophorbide a or methylpyrophæophorbide a yielded devinylpyrophæophorbide and the same reaction was applied to chlorin e_6 and chlorin e_4. Unsuccessful attempts were made to prepare compounds related to bacteriochlorophyll by subsequent acetylation. The following γ-derivatives of pyrroporphyrin are described : CN, $CH_2 \cdot OH$, $CO \cdot CO_2 Me$, $CH(OH) \cdot CO_2 Me$;[37] $CO_2 H$, $CO \cdot NH_2$;[40] γ-cyanopyrrochlorin has been prepared from (XIX).[53] 6-Cyano-pyrro- and -phyllo-porphyrins have been made from the corresponding bromoderivatives; the saponification of the former constitutes a new synthesis of rhodoporphyrin.[39] Phæoporphyrin a_5 dimethyl ester has been reduced to its deoxo-derivative.[37] A. Stern [58] emphasises the similarity in type of the fluorescence spectra of chlorins and porphyrins. Bonelline, the pigment of *Bonellia viridis*, has been purified and is conjecturally regarded as $6 : \gamma$-dihydroxymesopyrrochlorin.[59]

Other Porphyrins.

"*Synthetic Rhodins*" and *Verdins*.—When a porphinpropionic acid is treated with oleum, or chlorosulphonic acid,[60] ring-closure takes place between the carboxyl group and the neighbouring *meso*-position. Further study [61] of the reaction shows that mesoporphyrin IX yields a mixture of isomerides :

$$P\begin{cases} Et\,(2) \\ [CH_2]_2 \cdot CO_2 H\,(6) \\ H\,(\gamma) \\ [CH_2]_2 \cdot CO_2 H\,(7) \end{cases} \qquad P\begin{cases} Et \\ [CH_2]_2 \,\rule{0.5cm}{0.4pt} \\ CO \,\rule{0.5cm}{0.4pt} \\ [CH_2]_2 \cdot CO_2 H \end{cases} + P\begin{cases} Et \\ [CH_2]_2 \cdot CO_2 H \\ CO \,\rule{0.5cm}{0.4pt} \\ [CH_2]_2 \,\rule{0.5cm}{0.4pt} \end{cases}$$
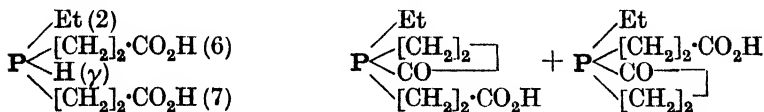
These "rhodins" * are readily converted into green *verdins*, formerly regarded as their enolic tautomerides. By the use of symmetrically substituted propionic acids pure crystalline materials have been obtained, and it has been shown that the verdin change

[56] *Z. physikal. Chem.*, 1939, *A*, **185**, 140.
[57] H. Fischer and A. Wunderer, *Annalen*, 1938, **533**, 230.
[58] *Z. physikal. Chem.*, 1938, *A*, **182**, 186.
[59] E. Lederer, *Compt. rend.*, 1939, **209**, 528.
[60] H. Fischer and H. Bock, *Z. physiol. Chem.*, 1938, **255**, 1.
[61] H. Fischer and C. G. Schröder, *Annalen*, 1939, **537**, 250; **541**, 196.

* The spectrum recalls that of rhodin g.

(best effected by semicarbazide hydrochloride in pyridine) involves isomerisation to a brown substance, followed by reversible dehydrogenation to the verdin :
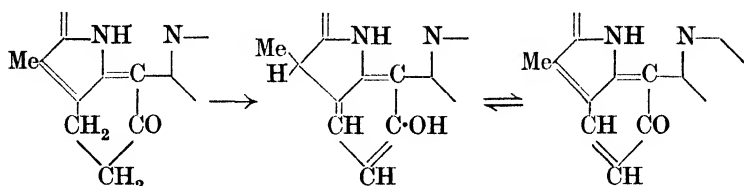
The brown intermediate shows only general absorption in accordance with the broken conjugation in the great ring. The carbonyl group of the verdin has been oximated in one case; oxidation at the adjacent double bond leads first to the glycol, and thence in the appropriate instance to the complete synthesis of the well-known " green anhydride " (XXIV). Pyrroporphyrin-γ-propionic acid undergoes similar ring-closure at the vacant position 6, giving an *iso*rhodin and thence an *iso*verdin.

$$\text{(XXIV.)} \quad \mathbf{P}\begin{array}{l} \diagup \text{Et (2)} \\ \!\!\!-\text{CO (6)} \\ \diagdown \!\!\!\diagup\text{O} \\ \text{CO } (\gamma) \end{array} \qquad \mathbf{P}\begin{array}{l} \diagup\!\!\!\diagup \text{R}_2 \text{ (2 : 4)} \\ \!\!\!-[\text{CH}_2]_2 \!\cdot\! \text{CO}_2\text{H (6)} \quad \text{(XXV.)} \\ \diagdown \\ \text{H } (\gamma) \end{array}$$
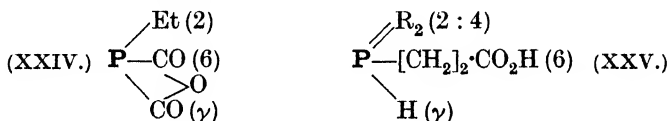
Possible Complexity of Hæmin.—Under both normal and pathological conditions, the symmetrical coproporphyrin I and uroporphyrin I may be excreted as well as their position isomerides of the series III, which correspond to the unsymmetrical natural hæmin. Speculation as to the source of these anomalous porphyrins has led to the re-examination of the homogeneity of the blood-pigment. Homogeneity was indicated by the apparent identity of the mixture of verdins from synthetic mesoporphyrin IX (XXV; R = Et) with that from mesoporphyrin made from hæmin, but H. Fischer states in a preliminary note [62] that the latter mesoporphyrin is indistinguishable from a 3 : 1 mixture of synthetic mesoporphyrins IX and II ; mesoporphyrin II corresponds to coproporphyrin I.

Porphyrin c.—Acid hydrolysis of the respiratory pigment cytochrome *c* affords a water-soluble porphyrin, porphyrin *c*, which is converted into hæmatoporphyrin IX (XXV; R = CHMe·OH) by hydrobromic acid.[63] H. Theorell showed [64] that a specially purified porphyrin *c* contained two sulphur atoms and two α-amino-acid residues and yielded *l*-cystine after hydrolysis,[65] but he discovered later that materials closely resembling porphyrin *c* were produced

[62] *Z. physiol. Chem.*, 1939, **259**, I.   [63] *Ann. Reports*, 1933, **30**, 250.
[64] *Biochem. Z.*, 1938, **298**, 242.   [65] *Enzymologia*, 1939, **6**, 88.

from cysteine and hæmato- or proto-porphyrin (XXV; R = CH:CH$_2$) but not mesoporphyrin, under the conditions of the original hydrolysis of cytochrome c. Finally K. Zeile and H. Meyer [66] have hydrolysed cytochrome c in very dilute solution to avoid synthesis of artefacts, and obtained a porphyrin c identical, except in optical rotation, with that produced by fusion of protoporphyrin hydrobromide with cysteine hydrochloride and regarded as [XXV; R = CHMe·S·CH$_2$·CH(NH$_2$)·CO$_2$H].

Miscellaneous.—F. Bandow [67] has examined the relative adsorption of porphyrins on various surfaces and its effect on their spectra. The partition of porphyrins between ether and hydrochloric acid has been studied more precisely.[68] Mesohæmin is best prepared by hydrogenation and subsequent aeration of hæmin.[69]

Linear Pigments.

Conversion of Porphyrins into Bilirubinoids.—R. Lemberg [70] showed that the " green hæmin " obtained by atmospheric oxidation of hæmin in presence of hydrazine is converted by methyl-alcoholic hydrochloric acid into dehydrobilirubin (IV below, with vinyl for Et) and that mesohæmin similarly afforded glaucobilin (IV). The coupled oxidation of pyridine hæmochromogen and ascorbic acid followed a similar course [71] and an intermediate product was characterised by its absorption maximum at 6390 A. The process is represented :

Hæmochromogen.   " 6390."   Verdo-hæmochromogen (or -hæmatin) = green hæmin.
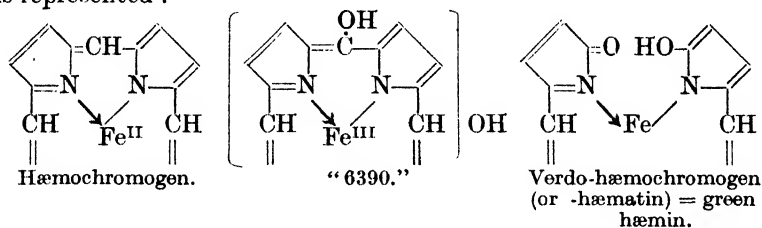
H. Fischer and H. Libowitzky [72] have oxidised the symmetrical coprohæmin I to a homogeneous coproglaucobilin (as IV) by both methods and also by the action of yeast. A hæmochromogen and green hæmin were intermediate products. The former, oxidised by hydrogen peroxide, gave an iron complex which yielded a blue pigment with a modified porphyrin spectrum. The iron complex

[66] *Naturwiss.*, 1939, **27**, 596.

[67] *Z. physikal. Chem.*, 1938, *B*, **39**, 155; 1939, *B*, **42**, 155; review by E. Lederer, *Bull. Soc. chim.*, 1939, **6**, 918.

[68] K. Zeile and B. Rau, *Z. physiol. Chem.*, 1937, **250**, 197; A. Keys and J. Brugsch, *J. Amer. Chem. Soc.*, 1938, **60**, 2135.

[69] T. H. Davies, *ibid.*, 1940, **62**, 447.   [70] *Biochem. J.*, 1935, **29**, 1322.

[71] R. Lemberg, B. Cortis-Jones, and M. Norrie, *ibid.*, 1938, **32**, 149, 171.

[72] *Z. physiol. Chem.*, 1938, **251**, 198; **255**, 209.

and the blue pigment afforded the same stable red acyl derivatives which had the spectral character of phylloporphyrin indicative of substitution at a bridge methin group, and were regarded as *ms*-acyloxyporphins, the iron compound being structurally analogous and the tautomeric ketodihydroporphin formula assigned to the blue substance. With pyridine and oxygen the iron complex yielded the " green hæmin," which these authors believe to be still a porphyrin. Photochemical oxidation of ætioporphyrin I [73] in presence of sodium ethoxide gave *inter alia* a glaucobilin; in pyridine several porphyrins appeared to undergo hydroxylation in the *ms*-positions.[60]

Nomenclature [74] *and Isomerism.*—The mother-substance $C_4H_4N \cdot [CH_2 \cdot C_4H_3N]_2 \cdot CH_2 \cdot C_4H_4N$ (as I) is termed *bilan* and the stages
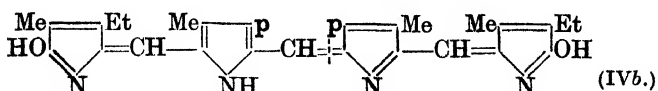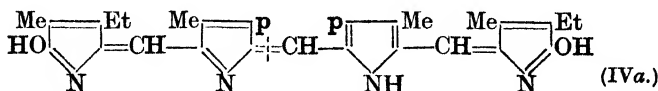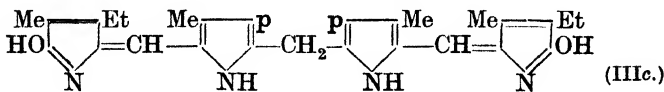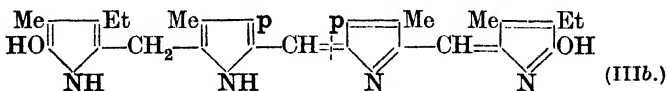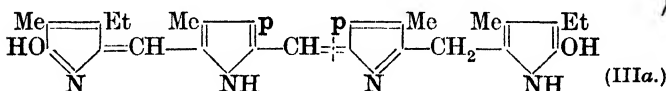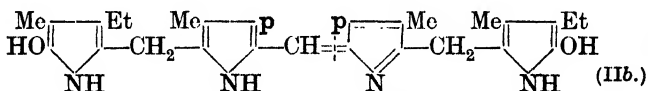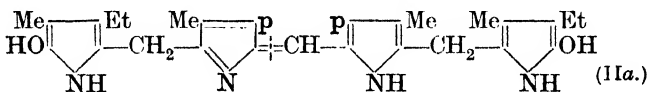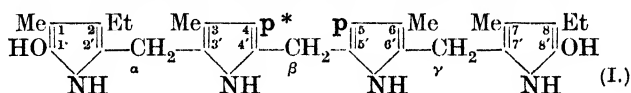
* $p = CH_2 \cdot CH_2 \cdot CO_2H(Me)$.

[73] H. Fischer and K. Herrle, *Z. physiol. Chem.*, 1938, **251**, 85.

[74] W. Siedel, *ibid.*, 1937, **245**, 257; ref. (3), p. 43.

of progressive dehydrogenation *biliene* (as II), *bilidiene* (as III), and *bilitriene* (*bilin*) (as IV). These substances exhibit tautomerism in respect of the hydrogen atoms of the imino-groups. Thus rational syntheses of (II*a*) and (II*b*) give the same product,[75] and similarly for (IV*a*) and (IV*b*); [76] but the isomerides (III*a*, *b*, *c*), differing in the position of the methylene group, are distinct compounds. Since the bilirubinoids have similar side-chains to those of the natural porphyrins, the orientation may also be indicated by comparison with the latter. For example, if the α-methin group were removed from the structure of mesoporphyrin IX and replaced by :O and ·OH, followed by enolisation, the resulting formula would be that of the glaucobilin (IV), which is therefore designated glaucobilin IXα.

Synthesis.—Methods are available for the synthesis of unsymmetrical bilirubinoids of all degrees of unsaturation. An α-aldehydo-dipyrryl-methane or -methene can be condensed with an α-free methane or methene—*i.e.*, either component may be at either stage of oxidation—to yield a tetrapyrrole pigment. Thus formyl-*neo*xanthobilirubic acid (V) (from hydrogen cyanide and *neo*-xanthobilirubic acid *) and *iso*neobilirubic acid yield (III*a*) : [76]

$$\text{Me}\overline{\quad}\text{Et}\ \text{Me}\overline{\quad}\text{p}$$
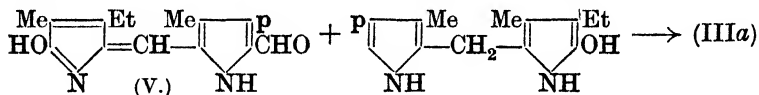
Similarly formyl*neo*bilirubic acid and *iso*neoxanthobilirubic acid give (III*b*); dotted lines in the formulæ indicate the analogous syntheses of (II*a* = II*b*) [75] and (IV*a* = IV*b*).[76] Symmetrical bilirubinoids with a central methin group have been prepared by treating α-free dipyrryl-methanes [75] or -methenes [76] with formic acid. A symmetrical bilitriene has also been obtained thus : [77]
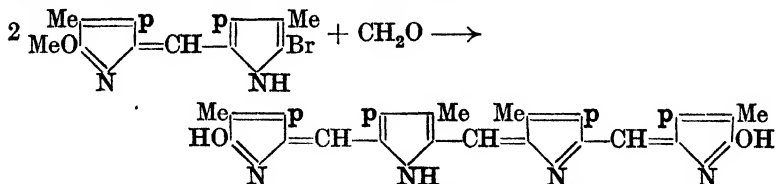
[75] W. Siedel and E. Meier, *Z. physiol. Chem.*, 1936, **242**, 101.

[76] W. Siedel, *ibid.*, 1935, **237**, 8.

[77] H. Fischer and A. Stachel, *Z. physiol. Chem.*, 1939, **258**, 121.

* Bilirubic acid is (A); the prefix *xantho* indicates oxidation to the methene, *neo* lack of the α-methyl group, and *iso* the different orientation corresponding to the right-hand half of the bilirubin system.
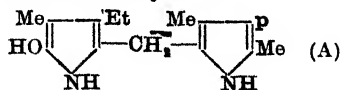
The final synthetic proof of the arrangement of side-chains in bilirubin was provided by the synthesis [74] of its reduction product mesobilirubin (IIIc). The aldehyde (V) was hydrogenated to the alcohol, without affecting the methene system, and the alcohol condensed with *isoneo*xanthobilirubic acid.
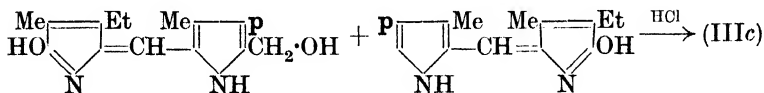
By fusing bilirubin with resorcinol, H. Fischer and H. Reinecke [78] obtained the acid (VI), which permitted the synthesis of a bilirubinoid having vinyl side-chains. With formaldehyde it gave a product, presumably (VII), closely resembling bilirubin. The same authors [79] have prepared by total synthesis a pigment with nitrovinyl groups.
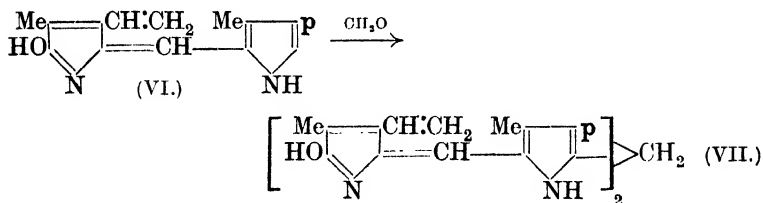
Bilirubin and Other Bilidienes.—It is usual to assign the formula (VIII) to bilirubin, which has four hydrogen atoms fewer than mesobilirubin (IIIc) and yields no methylethylmaleinimide on oxidation. On the other hand the modification (IX) has been advanced [78, 80] for the following reasons : nitrous acid oxidises bilirubin to a substance which is regarded as (XI), since it is hydrogenated to a material isomeric with methylethylmaleinimide ; the hydrogenation of bilirubin exhibits a marked discontinuity at the dihydro-stage, indicating an unsymmetrical structure, confirmed by the homogeneity of (VI), which yields on reduction *neo*xantho- and *neo*bili-rubic acids *free from their isomerides*. But the structure and even the existence of the " nitrite body " (XI) have been questioned ; [70] the properties of (VII) support the formulation of bilirubin as (VIII) ; and since dihydrobilirubin is (X),* structure (IX) for bilirubin implies a most unlikely

[78] *Z. physiol. Chem.*, 1938, **258**, 9.

[79] *Ibid.*, p. 243.

[80] H. Fischer and H. W. Haberland, *ibid.*, 1935, **232**, 236.

* Because resorcinol fusion yields exclusively *isoneo*xanthobilirubic acid.

hydrogenation of the CH_2–O bond in preference to the vinyl group.

(VIII.)

(IX.)   (X.)   (XI.)
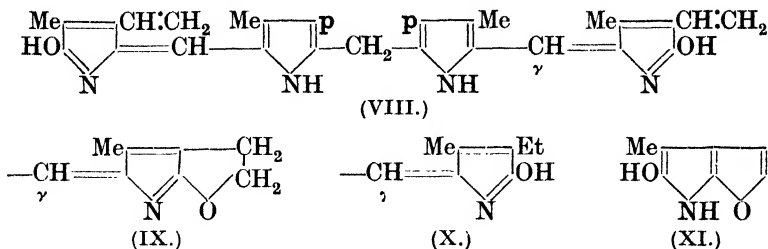
The absorption of bilidienes with a central methylene group is similar to that of xanthobilirubic acids, but intensified in proportion to their two dipyrrylmethene units.[81, 82]

Mesobiliviolin, which is produced by the oxidation of mesobilirubinogen (I) by ferric chloride and closely resembles copromesobiliviolin from fæces, has been separated chromatographically into mesobiliviolin proper (IIIa) and mesobilirhodin (IIIb), and both pigments synthesised.[76]

Stercobilin.[83]—Fæces and some pathological urines afford this pigment, $C_{33}H_{46}O_6N_4$,[84] which is strongly lævorotatory, and gives no pyrrole derivatives on reduction and neither hæmatic acid nor methylethylmaleinimide on oxidation. It yields a leuco-compound distinct from mesobilirubinogen, but concentrated sulphuric acid converts it into glaucobilin (IV), and the rather improbable formula (XII) is assigned to it. It appears that the zinc acetate reaction of pathological urines attributed to urobilin (II) is due, in most cases at least, to stercobilin.[85]

(XII.)
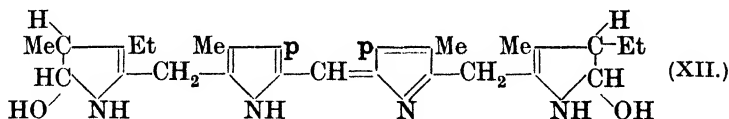
Bilichrysenes.—R. Lemberg and W. H. Lockwood,[86] who reserve the term (meso)biliviolin for the substances produced in the violet stage of the Gmelin reaction, find that oxidation of glaucobilin with iodine and zinc acetate yields the zinc salt of unstable mesobiliviolin II, which on standing affords *mesobilichrysin*. This yellow

[81] A. Stern and (Frl.) F. Pruckner, *Z. physikal. Chem.*, 1938, *A*, **182**, 117.

[82] L. Heilmeyer, H. Geiger, and R. Schultze, *Biochem. Z.*, 1937, **294**, 90.

[83] H. Fischer and H. Halbach, *Z. physiol. Chem.*, 1936, **238**, 59; H. Fischer and H. Libowitzky, *ibid.*, 1939, **258**, 255.

[84] Contrast ref. (82).

[85] R. Lemberg, *Ann. Rev. Biochem.*, 1938, **7**, 436.

[86] *J. Proc. Roy. Soc. N.S.W.*, 1939, **72**, 69.

pigment, $C_{33}H_{38}O_7N_4$, shows no absorption band and is regarded as a ketone; further oxidation gives a mesobiliviolin III, characterised, like the other, by its spectrum. Biliverdin yields a similar bilichrysin. In the photochemical oxidation of ætioporphyrin I, H. Fischer and K. Herrle [73] isolated a product which they regarded as a ketobilidiene.

Other Polynuclear Pigments.—Catalytic reduction [77] of a bromo-dipyrrylmethene yielded the pigment (XIII), which closely resembled the bilirubinoids in its colour reactions, as did synthetic hexa-pyrrenes [87] of the type

$$C_4H_3N:CH \cdot C_4H_3N \cdot CH_2 \cdot C_4H_2N:CH \cdot C_4H_3N \cdot CH_2 \cdot C_4H_3N \cdot CH:C_4H_3N.$$
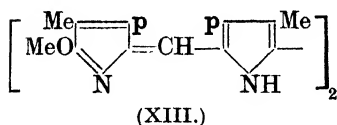
Several tripyrrenes have been made [88] by the methods indicated for (XIV). Their resemblance to the products of the violet phase of the Gmelin test suggests that this may involve the formation of tripyrrenes.

$$\left[\begin{array}{c} \text{Me} \quad \text{p} \quad \text{p} \quad \text{Me} \\ \text{MeO} \quad =\text{CH}- \\ \text{N} \qquad \text{NH} \end{array} \right]_2$$

(XIII.)

(XIV.)
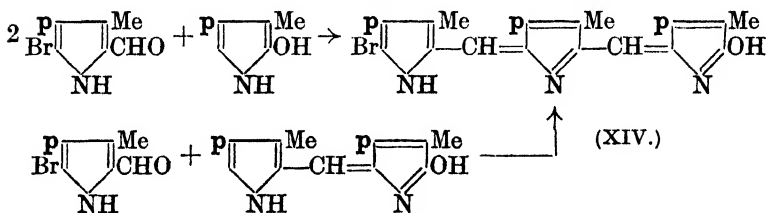
Dipyrrylmethenes.—The reduction of *crude* bilirubin with sodium amalgam yielded a material termed "Körper II," which has now been purified chromatographically.[89] Analysis and molecular weight determinations support the formula $C_{17}H_{22}O_4N_2$, and oxidation affords methylethylmaleinimide and hæmatic acid. The same material is produced by oxidising mesobilirubinogen with lead tetra-acetate, and by reduction of E. Weinberger's *bilifuscin* [90] from human gall-stones, whence it is renamed mesobilifuscin. Lead tetra-acetate oxidises *neo*xanthobilirubic acid to a colourless substance (XV), reducible to a mesobilifuscin (XVI). The original Körper II is regarded as a mixture of (XVI) and its position isomeride related to *iso*neoxanthobilirubic acid. A similar or identical pigment occurs as a protein complex in the fæces of myopathic patients.[91]

[87] H. Fischer and H. Reinecke, *Z. physiol. Chem.*, 1938, **251**, 204.

[88] *Idem, ibid.*, 1939, **259**, 83; for Gmelin test see ref. (80) and W. Siedel, *Angew. Chem.*, 1939, **52**, 38.

[89] W. Siedel and H. Möller, *Z. physiol. Chem.*, 1939, **259**, 113.

[90] *Ibid.*, 1936, **238**, 124.

[91] G. Meldolesi, W. Siedel, and H. Möller, *ibid.*, 1939, **259**, 137.

It appears [89, 92] that related materials are responsible for the "pentdyopent" reaction [development of an absorption band at

$$\underset{\text{N}}{\underset{\text{HO}}{\text{Me}}}\!\!=\!\!\text{Et}\ \underset{\text{NH}}{\underset{\text{Me}}{}}\!\!\text{P} \longrightarrow \underset{\text{NH}}{\underset{\text{HO}}{\text{Me}}}\!\!=\!\!\text{Et}\ \underset{\text{NH}}{\underset{\text{OH}}{\text{Me}}}\!\!\text{P} \quad (\text{XV.}) \longrightarrow$$

$$\underset{\text{N}}{\underset{\text{HO}}{\text{Me}}}\!\!=\!\!\text{Et}\ \underset{\text{NH}}{\underset{\text{OH}}{\text{Me}}}\!\!\text{P} \quad (\text{XVI.})$$

Me═══Et Me───P → Me───Et Me───P →
HO └─┘═CH—CH— └─┘ NH   HO └─┘—CO— └─┘OH
   N   NH   NH (XV.) NH

                    Me═══Et Me───P
                    HO └─┘═CH— └─┘OH
                       N (XVI.) NH
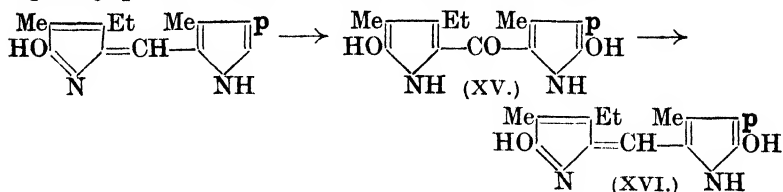
5250 A. after treatment with sodium hyposulphite (dithionite) and alkali] given by pathological urines, and by hæmin and bile pigments after degradation by hydrogen peroxide. *neo*Xanthobilirubic acid in this way gives a "pentdyopent," but the homologous xanthobilirubic acid does not; 5 : 5'-dibromodipyrrylmethenes react with loss of both bromine atoms, and diamino- and aminohydroxy-methenes respond after treatment with nitrous acid. It is inferred that the reaction involves the formation of a 5 : 5'-dihydroxydipyrrylmethene, and since (XVI) gives a very intense colour it is suggested that pentdyopents are the sodium salts of dihydroxydipyrrylcarbinols. Owing to the different possible directions of ring-fission, hæmin yields basic as well as acidic pentdyopents on degradation.

The mechanism of the synthesis of dipyrrylmethenes is controversial. The following anomalous reaction (writing P and Q indifferently for pyrroles and the univalent α-pyrryl and bivalent α-pyrrolene radicals) $— \text{P·CHO} + 2\text{Q} \longrightarrow \text{P} + \text{Q·CH:Q}$—is attributed by Fischer [93] to transference of the formyl group from P to Q. Corwin concludes that the methenes are formed according to the following scheme :

$$\text{P·CHO} + \text{P} \overset{1}{\longrightarrow} \text{P·CH:P}; \quad \text{P·CH:P} + \text{P} \underset{3}{\overset{2}{\rightleftharpoons}} \text{CHP}_3$$
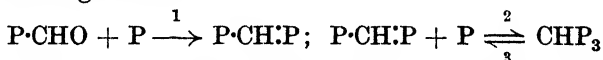
He has shown that, in the cases studied, the reaction velocities are in the order $2 > 1 > 3$; and that brief interaction of equimolecular quantities of aldehyde and free pyrrole gives nearly quantitatively tripyrrylmethane and excess of aldehyde, whereas more prolonged treatment gives an excellent yield of methene. Acid displaces the equilibria in favour of methene as the only basic product, and it is shown that an unsymmetrical tripyrrylmethane may break down in all three possible ways.[94]

[92] H. Fischer and A. Müller, *Z. physiol. Chem.*, 1937, **246**, 43; H. Fischer, H. Reinecke, and H. Lichtenwald, *ibid.*, 1939, **257**, 190; ref. (3), p. 397.

[93] H. Fischer and P. Ernst, *Annalen*, 1926, **447**, 139; W. Metzger and H. Fischer, *ibid.*, 1936, **527**, 1; H. Fischer and E. Strobel, *ibid.*, 1937, **531**, 251.

[94] A. H. Corwin and J. S. Andrews, *J. Amer. Chem. Soc.*, 1936, **58**, 1086; 1937, **59**, 1973; J. H. Paden, A. H. Corwin, and W. A. Bailey, *ibid.*, 1940, **62**, 418.

Using α-pyrryl ketones, H. Fischer and H. Höfelmann [95] have prepared *ms*-methyldipyrrylmethenes which are unstable, especially as free bases; but A. H. Corwin and W. M. Quattlebaum [96] obtained no *N*-methylated methenes by condensation of *N*-methylpyrroles with pyrrole aldehydes or formic acid, by oxidation of *N*-methyl-dipyrrylmethanes, by bromination of *NC*-dimethylpyrroles, or by methylation of dipyrrylmethenes.   T. S. S.

7. STEROIDS.

(Continued from *Ann. Reports*, 1936, **33**, 341 ; 1938, **35**, 281.)

This Report does not include a review of attempts at complete synthesis of steroids, but reference must be made to the successful total synthesis of *d*-equilenin (I) and its three stereoisomers (the antipode *l*-equilenin and the diastereoisomers *d*- and *l-iso*equilenin) by W. E. Bachmann, W. Cole, and A. L. Wilds,[1] an achievement which has been described by E. A. Doisy [2] as " one of the outstanding accomplishments in the sex-hormone field." *d*-Equilenin, an œstrogenic hormone isolated from the urine of pregnant mares by A. Girard, G. Sandulesco, A. Fridenson, and I. J. J. Rutgers,[3] is thirteen times as active as its antipode, *l*-equilenin. The synthetic diastereoisomer, *d-iso*equilenin, is identical with the 14-*epi*equilenin recently prepared by H. Hirschmann and O. Wintersteiner [4] from equilin ; *d*- and *l-iso*equilenin are less potent œstrogenic agents than either form of equilenin.

Androstane Derivatives.

Androstenedione has been directly reduced to testosterone by the Meerwein–Ponndorff method.[5] The observation of K. Miescher and E. Tschopp,[6] that 17-methyltestosterone [7] is the most active male hormone (rat test), has been followed by the preparation of

[95] *Z. physiol. Chem.*, 1938, **251**, 218; compare W. Siedel, *ibid.*, 1935, **231** 177.

[96] *J. Amer. Chem. Soc.*, 1936, **58**, 1081.

[1] *J. Amer. Chem. Soc.*, 1940. **62**, 824.   [2] *Nature*, 1940, **146**, 624.

[3] *Compt. rend.*, 1932, **195**, 981.   [4] *J. Biol. Chem.*, 1938, **126**, 747.

[5] K. Miescher and W. H. Fischer, *Helv. Chim. Acta*, 1939, **22**, 158; see also *B.*, 1940, 324 (P).

[6] *Schweiz. med. Woch.*, 1938, **68**, 1258.

[7] L. Ruzicka, M. W. Goldberg, and H. R. Rosenberg, *Helv. Chim. Acta*, 1935, **18**, 1495; A. D. Tschinaeva, M. I. Uschakov, and A. T. Martschevski, *J. Gen. Chem. Russia*, 1939, **9**, 1865; G. I. Kiprianov and B. E. Frenkel, *ibid.*, p. 1682; K. Fujii and T. Matsukawa, *J. Pharm. Soc. Japan*, 1935, **55**, 1333; 1936, **56**, 158; S. Kuwada and M. Miyasaka, *ibid.*, 1939, **58**, 59.

17(epi)-methyltestosterone;[8] it is relatively inactive (capon or rat tests).   K. Miescher and A. Wettstein[9] have also prepared the isomeric 17-hydroxymethyl-Δ^4-androsten-3-one.   A noteworthy synthesis of 16-hydroxytestosterone (II) has been reported by A. Butenandt, J. Schmidt-Thomé, and T. Weiss.[10]   This substance is the male hormone counterpart of the œstrogenic hormone œstriol (III).   Tests show that, although 16-hydroxytestosterone has considerably less male-hormone activity than testosterone (Fussgänger test), unlike the latter it is a fairly potent œstrogenic agent.   The implications of these tests are complicated by the fact that the orientation of the 17-hydroxyl group in 16-hydroxytestosterone is not known ; it may be the same as or different from that in testosterone.

(I.)   (II.)   (III.)
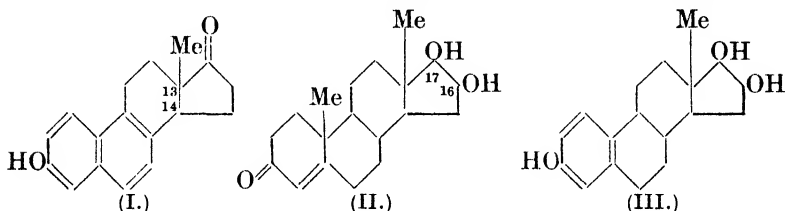
3(β) : 6-Dihydroxyandrostan-17-one has been obtained, together with *allo*hyodeoxycholic acid, by the oxidation of 3 : 6-diacetoxy-cholestane.[11]   The isomeric 17-hydroxy-Δ^4-and-Δ^5-androstenes have been prepared by R. E. Marker, E. L. Wittle, and B. F. Tullar.[12]

The unsaturated diketone obtained by treatment of 2-bromo-androstane-3 : 17-dione with potassium acetate,[13] previously assumed to be Δ^1-androstenedione (IV), has been shown to be incorrectly described ; the true Δ^1-androstenedione (IV) has now been obtained by treatment of 2-bromoandrostanedione with collidine ;[14] its physiological activity is of interest.   When tested by the Fussgänger technique, it is an extremely active male hormone, whereas in the capon test it has only one-fifth the activity of testosterone.

The ultra-violet irradiation of a solution of 3 : 17-dihydroxy-$\Delta^{5:7}$-androstadiene (V, R = OH),[15] which differs from ergosterol (pro-vitamin-D_2) (V, R = C_9H_{17}) in the nature of the groups associated

[8] K. Miescher and W. Klarrer, *Helv. Chim. Acta*, 1939, **22**, 962.

[9] *Ibid.*, p. 1262.   [10] *Ber.*, 1939, **72**, 417.

[11] R. E. Marker, J. Krueger, J. R. Adams, and E. M. Jones, *J. Amer. Chem. Soc.*, 1940, **62**, 645.

[12] *Ibid.*, p. 223.

[13] A. Butenandt and H. Dannenberg, *Ber.*, 1936, **69**, 1158.

[14] A. Butenandt, L. Mamoli, H. Dannenberg, L. W. Masch, and J. Paland, *ibid.*, 1939, **72**, 1617; see also R. P. Jacobsen, *J. Amer. Chem. Soc.*, 1940, **62**, 1620.

[15] A. Butenandt, E. Hausmann, and J. Paland, *Ber.*, 1938, **71**, 1316; A. Butenandt and J. Paland, *ibid.*, 1939, **72**, 424.

with C_{17}, has been examined by K. Dimroth and J. Paland.[16]   The alteration in the ultra-violet absorption spectrum of the solution exactly parallels that observed in the case of ergosterol, the inference being that the diol gives a similar series of photo-isomers.   The irradiation product from the diol does not exhibit antirachitic activity.

An interesting conversion of $3(\beta)$-hydroxy-Δ^5-steroid derivatives into the corresponding Δ^4-3-ketones is claimed in a patent; [17]
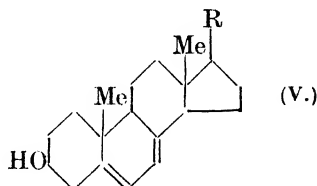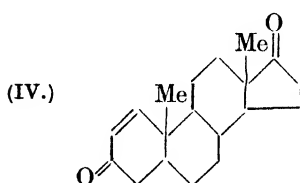
the 3-triarylmethyl ethers of dehydroandrosterone and of androstenediol, when heated, give androstenedione and testosterone respectively.

Synthesis of Pregnane from Androstane Derivatives.

T. Reichstein and K. Gätzi [18] postulated that the naturally occurring adrenal steroids of the 3 : 17-dihydroxypregnane series have a common configuration at C_{17} [17(β)-hydroxy] and that this differs from the configuration [17(α)-hydroxy] pertaining in the products obtained by the interaction of 17-ketoandrostane derivatives with ethylmagnesium halides, or with acetylene.   The last reaction has been re-examined by T. Reichstein and C. Meystre; [19] addition of acetylene to 3(β)-hydroxyandrostan-17-one (VI) gives 3(β) : 17(α)-dihydroxy-17-ethinylandrostane (VII) [20] as major product together with a small quantity of the isomeric 3(β) : 17(β)-diol (VIII).   Ozonolysis of the 3-monoacetate of (VIII) gave 3(β) : 17(β)-dihydroxy*allo*ætiocholanic acid (IX), which proved to be identical with the acid obtained by T. Reichstein and K. Gätzi [18] by oxidation of the adrenal substance P with periodic acid, thus establishing that this substance and the related substance K are 17(β)-hydroxy*allo*pregnane derivatives.   The major product of the interaction of dehydroandrosterone (X) and acetylene is the 3(β) : 17(α)-diol (XI); [20] the isomeric 3(β) : 17(β)-diol (XII) has now been isolated from the reaction product.   This was correlated with the 3(β) : 17(β)-diol (VIII) by hydrogenation of both products to the same saturated

[16] *Ber.*, 1939, **72,** 187.   [17] *B.*, 1940, 566.
[18] *Helv. Chim. Acta*, 1938, **21,** 1185.   [19] *Ibid.*, 1939, **22,** 728.
[20] L. Ruzicka and K. Hofmann, *ibid.*, 1937, **20,** 1280;   J. Kathol, W. Logemann, and A. Serini, *Naturwiss.*, 1937, **25,** 682.

3(β) : 17(β)-dihydroxy*allo*pregnane (XIII). Addition of bromine to protect the Δ^5-linkage, followed by ozonolysis and debromination,
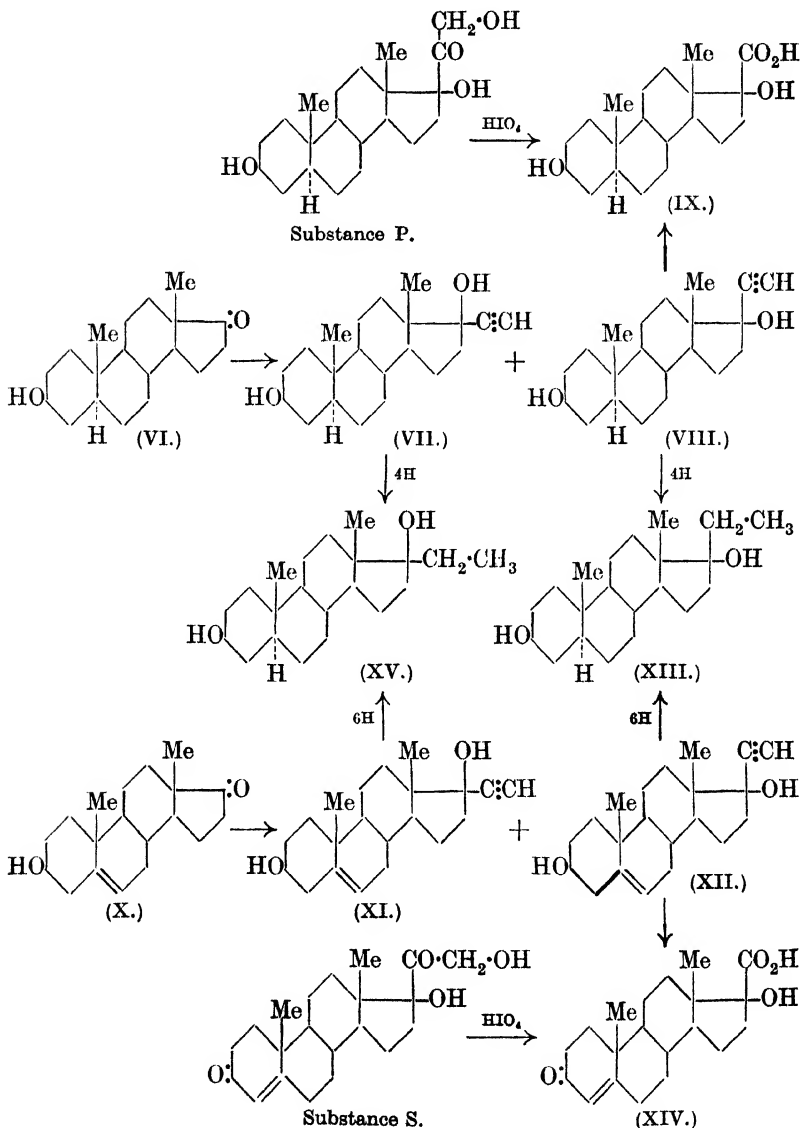
converted (XII) into 3(β) : 17(β)-dihydroxy-Δ^5-ætiocholenic acid, oxidation of which (Oppenauer) gave the corresponding αβ-unsatur-

ated keto-acid (XIV),[21] which was shown to be identical with the acid obtained by treatment of the adrenal substance S with periodic acid.[22]   In conformity with the previous observations of T. Reichstein and K. Gätzi,[18] the $3(\beta) : 17(\beta)$-diols (VIII), (XII), and (XIII) give insoluble digitonides, a behaviour not exhibited by the $3(\beta) : 17(\alpha)$-diols (VII) and (XI) and their common hydrogenation product (XV).

That the addition of hydrogen cyanide to 17-ketoandrostane derivatives gives $17(\alpha)$-hydroxyandrostane derivatives has been amply confirmed by K. Miescher and A. Wettstein.[23]

The structures ascribed to a number of adrenal steroids from their behaviour on degradation have been confirmed by partial syntheses. A. Serini, W. Logemann, and W. Hildebrand [24] have prepared the adrenal substance K (XVIII) [18] from $3(\beta) : 17(\alpha)$-dihydroxy-Δ^{20}-*allo*pregnene (XVI); the latter was isomerised by the method of
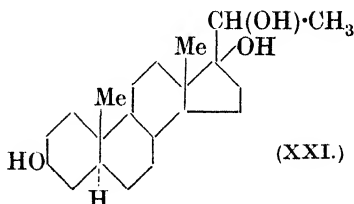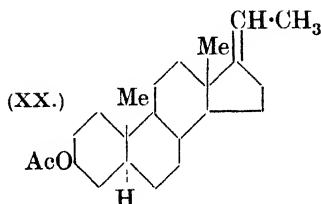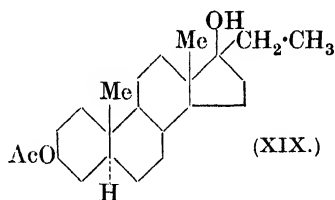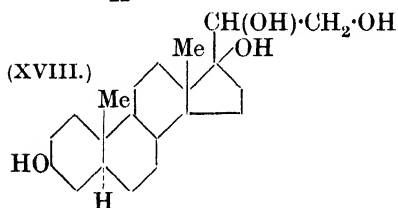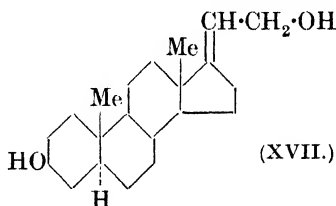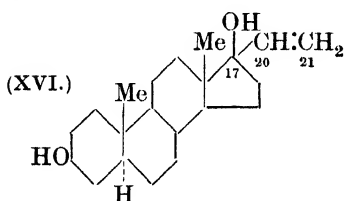
K. Dimroth [25] to $3(\beta) : 21$-dihydroxy-Δ^{17}-*allo*pregnene (XVII), hydroxylation of which with osmium tetroxide (Criegee) [26] gave substance K.   The interesting observation is thus made that this method of

[21] T. Reichstein, C. Meystre, and J. v. Euw, *Helv. Chim. Acta*, 1939, **22**, 1107.

[22] T. Reichstein, *ibid.*, 1938, **21**, 1490.

[23] *Ibid.*, 1938, **21**, 1317; 1939, **22**, 112.   [24] *Ber.*, 1939, **72**, 391.

[25] *Ibid.*, 1938, **71**, 1333.   [26] *Annalen*, 1936, **522**, 75.

hydroxylation of a Δ^{17}-linkage leads to a 17(β)-hydroxy-steroid; this is not an invariable rule, however.[27] Partial syntheses of the adrenal substances J and O have been completed by H. Reich, M. Sutter, and T. Reichstein.[27] Dehydration of 17(α)-hydroxy-3(β)-acetoxy*allo*pregnane (XIX) yielded 3(β)-acetoxy-Δ^{17}-*allo*pregnene (XX), which when hydroxylated by Criegee's method gave a mixture of three of the four possible stereoisomeric (C_{17} : C_{20}) triols (XXI), one, the major product, being identical with substance J[28] and a second, a minor product, being identical with substance O.[28]

Pregnene Aldehydes.—Of the large number of *allo*pregnane derivatives isolated from the adrenal cortex, five have been shown to be capable of maintaining the life of adrenalectomised animals. These are corticosterone, dehydrocorticosterone, 17-hydroxycorticosterone, 17-hydroxydehydrocorticosterone, and deoxycorticosterone with the possibility of a sixth in substance S. Although the " cortin activity " varies greatly according to the test method employed, deoxycorticosterone (and its esters) appears to be the most potent hormone; recent investigations,[29] however, show that it has clinical disadvantages in the treatment of Addison's disease when compared with the C_{11}-oxygenated cortical hormones. It has been persistently reported that after the separation of all crystalline components of adrenal extracts, the amorphous residue still possesses extremely high cortin activity[30] and it has been concluded that this amorphous residue contains a substance more physiologically potent than any hitherto isolated cortical hormone. H. Reich and T. Reichstein[31] observe that the amorphous concentrate may possibly owe its enhanced activity to the presence of an activator substance.

Since attempts to isolate a homogeneous substance from these concentrates have not been successful, an alternative approach to the problem has been the synthesis of pregnane derivatives closely related to deoxycorticosterone. For obvious reasons, much effort has been directed towards the synthesis of 21-pregnane aldehydes. Using the elegant method of F. Kröhnke and E. Börner,[32] the partial synthesis of Δ^4-pregnene-3 : 20-dion-21-al (XXIII) has been accomplished by H. Reich and T. Reichstein.[31] 21-Chloroprogesterone

[27] *Helv. Chim. Acta*, 1940, **23,** 170; M. Sutter, C. Meystre, and T. Reichstein, *ibid.*, 1939, **22,** 618.

[28] M. Steiger and T. Reichstein, *ibid.*, 1938, **21,** 546; T. Reichstein and K. Gätzi, *ibid.*, p. 1497.

[29] C. N. H. Long, B. Katzin, and E. G. Fry, *Endocrinology*, 1940, **26,** 309; D. J. Ingle, *ibid.*, p. 472.

[30] O. Wintersteiner and J. J. Pfiffner, *J. Biol. Chem.*, 1936, **116,** 291; W. M. Hoehn, H. L. Mason, and E. C. Kendall, *ibid.*, 1938, **124,** 459; E. C. Kendall, *ibid.*, 1939, **128,** li (Proc.).

[31] *Helv. Chim. Acta*, 1939, **22,** 1124.   [32] *Ber.*, 1936, **69,** 2006.

[prepared by the Oppenauer oxidation of 21-chloro-3(β)-hydroxy-Δ^5-pregnen-20-one] [33] was converted into the glyoxal (XXIII) by the following steps :
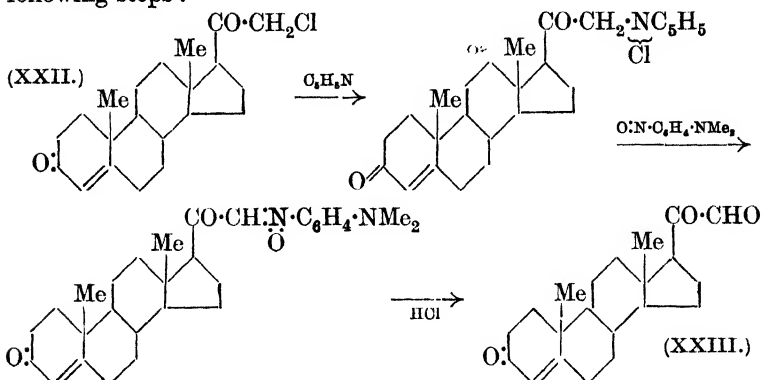
Preliminary biological tests show that the glyoxal has definite cortin activity.

Another route to 21-aldehydes of the pregnane series was opened by K. Miescher and C. Scholz [34] and independently by L. Ruzicka and P. Müller.[35] Miescher and Scholz prepared 3(β) : 21-dihydroxy-$\Delta^{5:17}$-pregnadiene (XXV; R = OH) by treatment of 3(β) : 17(α)-

dihydroxy-$\Delta^{5:20}$-pregnadiene (XXIV) [36] successively with acetic anhydride and trichloroacetic acid.[25] Similar treatment of 17(α)-hydroxy-$\Delta^{4:20}$-pregnadien-3-one [37] gave 21-hydroxy-$\Delta^{4:17}$-pregnadien-3-one (XXVI; R = OH). Ruzicka and Müller obtained (XXV, R = OH) by treatment of the 3-monoacetate of (XXIV) with phosphorus tribromide to give the bromide (XXV, R = Br) and subsequent
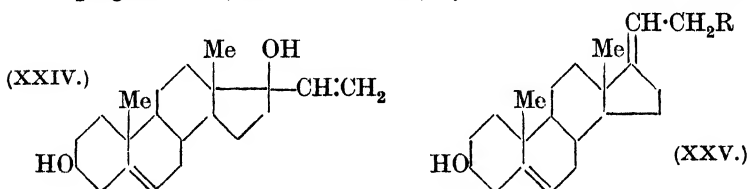
[33] M. Steiger and T. Reichstein, *Helv. Chim. Acta*, 1937, **20**, 1165.

[34] *Ibid.*, 1939, **22**, 120.   [35] *Ibid.*, p. 416.

[36] J. Kathol, W. Logemann, and A. Serini, *Naturwiss.*, 1937, **25**, 682; L. Ruzicka, K. Hofmann, and H. F. Meldahl, *Helv. Chim. Acta*, 1938, **21**, 371, 599; H. H. Inhoffen, W. Logemann, W. Hohlweg, and A. Serini, *Ber.*, 1938, **71**, 1032.

[37] L. Ruzicka, K. Hofmann, and H. F. Meldahl, *Helv. Chim. Acta*, 1938, **21**, 597.

treatment of this with potassium acetate.[38] In the same way
17(α)-hydroxy-$\Delta^{4:20}$-pregnadien-3-one gave the bromide (XXVI,
R = Br) and thence (XXVI, R = OH).

Controlled oxidation of (XXVI, R = OH) gave the keto-aldehyde
(XXVII),[39] which has also been obtained by H. Reich[40] by the
application of the Kröhnke method to the unsaturated bromide
(XXVI, R = Br). Using the same route and starting from the
acetate of the unsaturated bromide (XXV, R = Br), Reich obtained
3(β)-hydroxy-$\Delta^{5:17}$-pregnadien-21-al (XXVIII). The unsaturated
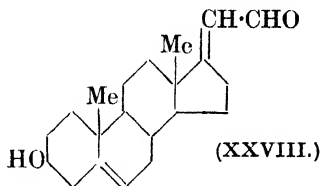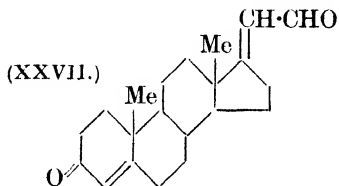
aldehydes (XXVII) and (XXVIII) have been prepared by an altern-
ative route by K. Miescher, A. Wettstein, and C. Scholz;[39]
3(β) : 17(α)-dihydroxy-17-allyl-Δ^5-androstene (XXIX)[41] was oxid-
ised to the corresponding Δ^4-3-ketone, and the synthesis completed
as follows :
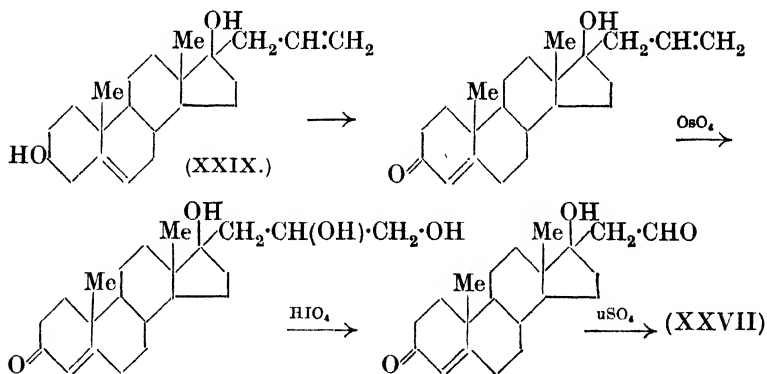
Oxidation of the acetate of (XXIX) with osmium tetroxide gave
a tetrol, side-chain and not nuclear hydroxylation occurring;
acetylation of the 3(β)-hydroxyl group protects the Δ^5-linkage from
attack by osmium tetroxide. By a similar procedure, the tetrol was
converted into the hydroxy-aldehyde (XXVIII).

[38] Compare L. Ruzicka and G. Firmenich, *Helv. Chim Acta*, 1939, **22**, 392.
[39] K. Miescher, A. Wettstein, and C. Scholz, *ibid.*, p. 894.
[40] *Ibid.*, 1940, **23**, 219.
[41] S. Kuwada and M. Yago, *J. Pharm. Soc. Japan*, 1936, **56**, 625; A.
Butenandt and D. Peters, *Ber.*, 1938, **71**, 2688.

Progesterone and Deoxycorticosterone.—Bromination of *allo*-pregnane-3 : 20-dione yields the 2-bromo-derivative (XXX);[42] R. E. Marker, E. L. Wittle, and L. Plambeck[43] have shown that this gives a pyridinium salt, distillation of which gives a mixture of progesterone (XXXI) and Δ^1-*allo*pregnenedione (XXXII). The latter differed from the unsaturated diketone originally claimed to have this structure by A. Butenandt and L. Mamoli,[42] but recently shown to be incorrectly designated.[14]

(XXXII.)   (XXX.)   (XXXI.)
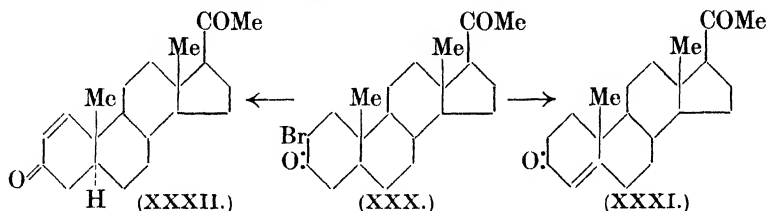
R. E. Marker and J. Krueger[44] established that oxidation of 3-hydroxy-6-acetoxycholestane (obtained by partial hydrolysis of 3 : 6-diacetoxycholestane) to 3-keto-6-acetoxycholestane, followed by hydrolysis and dehydration, yielded Δ^4-cholestenone. This series of reactions was employed by these authors to convert hyodeoxycholic acid into progesterone. A route to progesterone *via* lithocholic acid by known processes has been opened by W. M. Hoehn and H. L. Mason,[45] who have prepared this acid in 50% yield from deoxycholic and cholic acids. The conversion of 3-hydroxybisnorcholenic acid (using the Curtius degradation) into progesterone is described by G. Ehrhart, H. Ruschig, and W. Aumüller.[46]

The synthesis of progesterone from dehydroandrosterone has been completed by A. Butenandt and J. Schmidt-Thomé.[47] The unsaturated nitrile (XXXIII) was converted into Δ^5-pregnenolone (XXXIV) as follows :

(XXXIII.)   (XXXIV.)
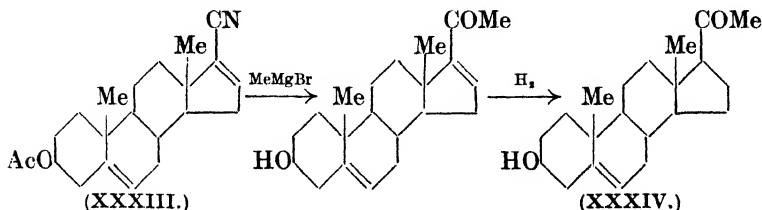
[42] A. Butenandt and L. Mamoli, *Ber.*, 1935, **68**, 1847.

[43] *J. Amer. Chem. Soc.*, 1939, **61**, 1333.

[44] *Ibid.*, 1940, **62**, 79; see also T. Kimura and G. Sugiyama, *J. Biochem. Japan*, 1939, **29**, 409.

[45] *J. Amer. Chem. Soc.*, 1940, **62**, 569.

[46] *Angew. Chem.*, 1939, **52**, 365.   [47] *Ber.*, 1938, **71**, 1487; 1939, **72**, 182.

The oxidation of (XXXIV) to progesterone has been previously described.[48]

A second (partial) synthesis of progesterone from dehydroandrosterone is described by A. Butenandt, J. Schmidt-Thomé, and H. Paul.[49] Dehydration of the 3-monoacetate of 3 : 17-dihydroxy-17-ethyl-Δ^5-androstene (XXXV)[50] gave 3-acetoxy-$\Delta^{5 : 17}$-pregnadiene (XXXVI), oxidation of which with osmium tetroxide gave the Δ^5-pregnenetriol (XXXVII), the 3 : 20-diacetate of which on distillation with zinc dust[51] gave 17-isopregnenolone (XXXVIII) (as acetate) identical with that prepared by the alkali isomerisation of Δ^5-pregnenolone.[52] Oxidation of (XXXVIII) (Oppenauer) gives isoprogesterone (XXXIX), which is readily isomerised by acids to progesterone (XXXI).
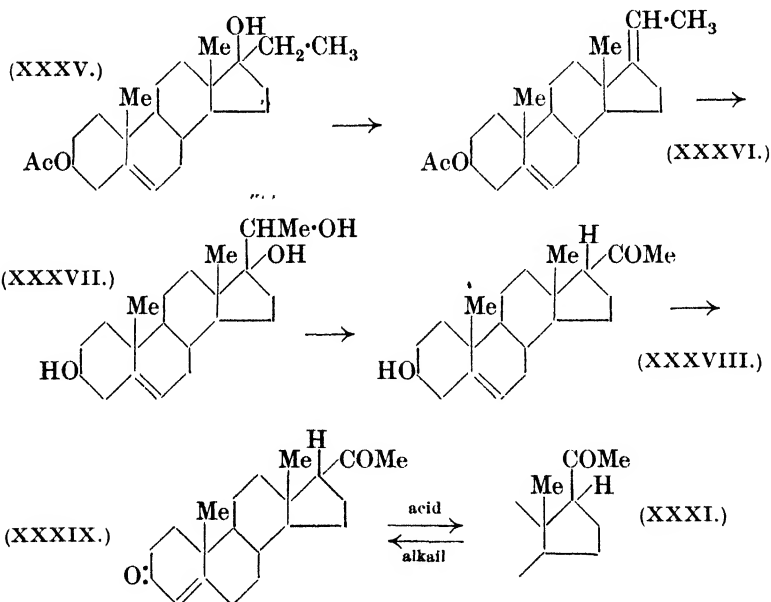
Hydration of the triple bond of 3(β) : 17(α)-dihydroxy-17-ethinyl-Δ^5-androstene (XL) (without ring enlargement but with simultaneous dehydration) has been accomplished by M. W. Goldberg

[48] A. Butenandt, U. Westphal, and H. Cobler, Ber., 1934, 67, 1611. 2085; 1936, 69, 443.

[49] Ber., 1939, 72, 1112.

[50] A. Butenandt, H. Cobler, and J. Schmidt, Ber., 1936, 69, 448.

[51] Compare K. Slotta and K. Neisser, Ber., 1938, 71, 2345.

[52] A. Butenandt and G. Fleischer, Ber., 1937, 70, 96.

and R. Aeschbacher,[53] using mercury acetamide; the product, 3(β)-hydroxy-$\Delta^{5:16}$-pregnadien-20-one (XLI), has been converted into progesterone.

(XL.)   →   (XLI.)
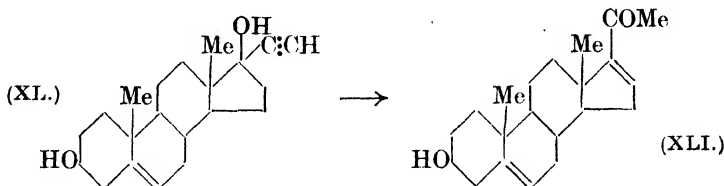
In view of the highly specific physiological activity of progesterone it is noteworthy that progestational activity has been claimed for three pregnane derivatives in addition to 17-ethinyltestosterone.[54] A. Wettstein [55] reports that 6-dehydroprogesterone (XLIII) has approximately half the progestational activity of progesterone. The preparation of (XLIII) was accomplished directly from Δ^5-pregnenolone (XLII) by a remarkable modification of the Oppenauer reaction, quinone being used as hydrogen acceptor. Progestational activity is also claimed for 6-hydroxyprogesterone [56] and for 21-hydroxyprogesterone (deoxycorticosterone).[57] 12-Hydroxy- [46] and

(XLII.)   →   (XLIII.)
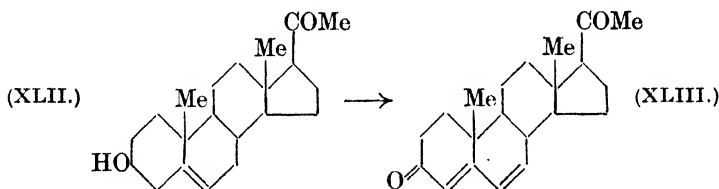
17(β)-hydroxy-progesterone, a recently isolated adrenal steroid,[58] have no progestational activity. Physiological tests on the isomeric hydroxyprogesterones described by G. Ehrhart, H. Ruschig, and W. Aumüller [59] are not reported.

The synthesis of deoxycorticosterone (XLIV) from dehydroandrosterone via 17-vinyltestosterone (XLIIIa) has been achieved

[53] Helv. Chim. Acta, 1939, 22, 1185.
[54] L. Ruzicka, K. Hofmann, and H. F. Meldahl, ibid., 1938, 21, 371.
[55] Ibid., 1940, 23, 388.
[56] M. Ehrenstein and T. O. Stevens, J. Org. Chem., 1940, 5, 318; M. Ehrenstein, ibid., 1939, 4, 506.
[57] J. Van Heuverswyn, V. J. Collins, W. L. Williams, and W. U. Gardner, Proc. Soc. Exp. Biol. Med., 1939, 41, 552.
[58] J. J. Pfiffner and H. B. North, J. Biol. Chem., 1940, 132, 461.
[59] Ber., 1939, 72, 2035.

by A. Serini, W. Logemann, and W. Hildebrand [60] by the following route :

(XLIIIa.) (XLIV.)
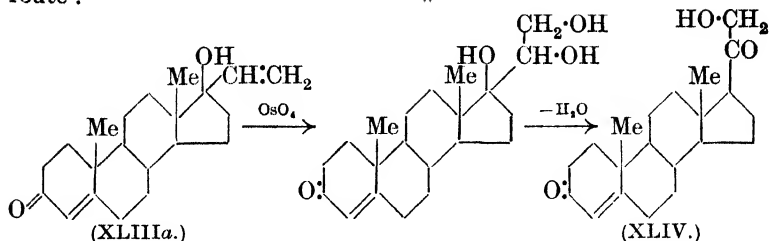
G. Ehrhart, H. Ruschig, and W. Aumüller [46] investigated the behaviour of pregnane ketones on oxidation with lead tetra-acetate. Δ^5-Pregnenolone acetate gives 3 : 21-diacetoxy-Δ^5-pregnen-20-one (XLV) and progesterone is converted into deoxycorticosterone in small yield.[61] Similar oxidation of 3(β)-acetoxy*allo*pregnan-20-one gives the 3(β) : 21-diacetoxy-derivative (XLVI) together with the triacetate of adrenal substance P (XLVII).[18]

A simplification of the T. Reichstein and M. Steiger [62] synthesis of deoxycorticosterone has been reported by T. Reichstein and J. v. Euw,[63] who find that the diazo-ketone (XLVIII) is remarkably

(XLV.)

(XLVI.)

(XLVII.)

(XLVIII.)
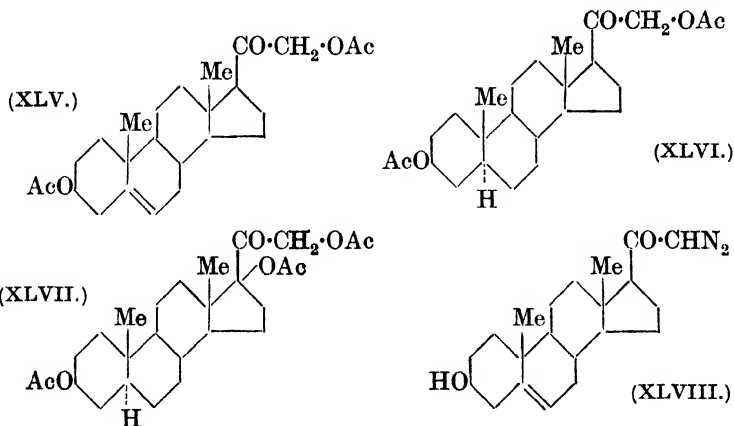
stable ; it can be oxidised in boiling benzene solution (Oppenauer) without decomposition of the diazoketonic group, yielding the corresponding Δ^4-3-ketone, treatment of which with aqueous mineral acid gives deoxycorticosterone.

[60] *Ber.*, 1939, **72**, 391.
[61] *Helv. Chim. Acta*, 1939, **22**, 1212; see also G. Ehrhart, H. Ruschig, and W. Aumüller, *Ber.*, 1939, **72**, 2035.
[62] *Ann. Reports*, 1938, **35**, 287.   [63] *Helv. Chim. Acta*, 1940, **23**, 136.

D-*Homoandrostane Derivatives.*

The low efficiency of the original (partial) synthetic method for preparing progesterone greatly intensified investigations which had as their object the conversion of the readily available dehydroandrosterone into the *corpus luteum* hormone; the investigation of two possible routes has brought to light an interesting case of ring-enlargement.

K. Miescher and H. Kägi [64] showed that the acetate of dehydroandrosterone reacted with dichloropropionic ester and magnesium amalgam to give the chlorohydrin-ester (XLIX), which on treatment with alkali gave a mixture of glycido-acids (L), decarboxylation of which yielded Δ⁵-pregnenolone (LI) and an isomer, " *neo*pregnenolone." *neo*Pregnenolone was obtained independently by L. Ruzicka and H. F. Meldahl [65] from 17-hydroxy-3(β)-acetoxy-17-ethinyl-Δ⁵-androstene (LV), hydration of which by Nieuwland's method (acetic acid–acetic anhydride, mercuric oxide, and boron trifluoride) [66] yielded a product, considered to be 17-hydroxy-Δ⁵-pregnenolone.[67] Treatment of the 3-acetate of the latter with phosphorus tribromide, followed by zinc dust, gave *neo*pregnenolone. At this stage, three different substances apparently competed for

Me OH Cl
Me ————CMe·CO₂Et   Me ——O CMe·CO₂H
Me
AcO   (XLIX.)   →   HO   (L.)

COMe
Me
Me   (LI.)
HO
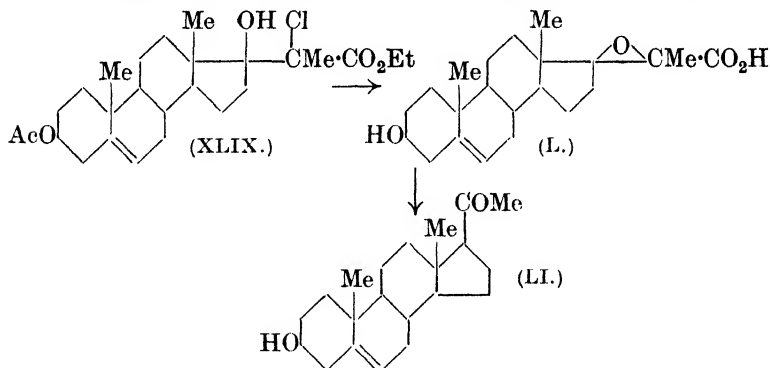
two possible structures, for in addition to normal Δ⁵-pregnenolone (LI), an *iso*pregnenolone had been obtained by A. Butenandt and G. Fleischer [52] by treatment of the normal ketone with alkali and assumed to differ from this in the orientation around C₁₇; oxidation of *iso*pregnenolone (with chromic acid) gave progesterone and not *iso*progesterone. K. Miescher and H. Kägi inclined to the view that *neo*pregnenolone is the true C₁₇-isomer of Δ⁵-pregnenolone and that the formation of *iso*pregnenolone is to be attributed to some other factor, possibly epimerisation around C₃. Interest in *neo*pregnen-

[64] *Helv. Chim. Acta*, 1939, **22**, 184.   [65] *Ibid.*, p. 421.
[66] G. F. Hennion, D. B. Killian, T. H. Vaughn, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 1130.
[67] L. Ruzicka and H. F. Meldahl, *Helv. Chim. Acta*, 1938, **21**, 1760.

olone became intense when it was reported that the corresponding ketone, *neo*progesterone, exhibited a pronounced progestational activity, a claim which has since been withdrawn.[55] The views of K. Miescher and H. Kägi on *iso*pregnenolone were shown to be ill-founded by A. Butenandt and A. Heusner,[68] who prepared the 3-epimer of Δ^5-pregnenolone, which differed from *iso*pregnenolone, and by A. Butenandt, J. Schmidt-Thomé, and H. Paul,[49] who prepared *iso*pregnenolone by an unambiguous method and showed that on oxidation (Oppenauer) it gave *iso*progesterone (p. 341).

The problem was solved by L. Ruzicka, K. Gätzi, and T. Reichstein,[69] who showed that *neo*pregnenolone and allied compounds prepared by the hydration of 17-hydroxy-17-ethinylandrostane

Me | OH | Me:C:CH
Me |
HO
H
(LII.)
→
Me | Me | OH | :O
Me |
HO
H
(LIII.)
→
Me | COMe | CO$_2$H
Me |
O:
H
(LIV.)
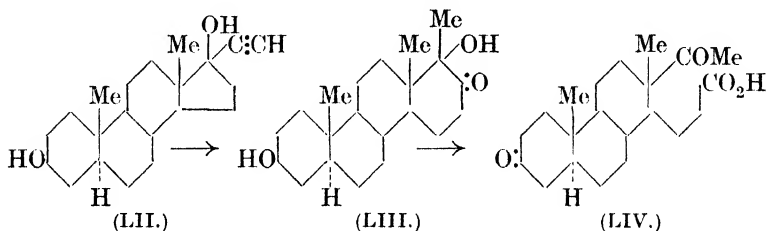
derivatives by the boron trifluoride–mercuric oxide method [65, 67, 70] are hydrochrysene derivatives, the reaction having effected enlargement of ring D. For example, hydration of 3(β) : 17(α)-dihydroxy-17-ethinylandrostane (LII) (as 3-monoacetate), followed by treatment with alkali, gives (LIII), a constitution established in its main principle by oxidation to a diketo-monocarboxylic acid (LIV). Similarly, the conversion of 3(β) : 17(α)-dihydroxy-17-ethinyl-Δ^5-androstene (LV) into *neo*pregnenolone (LVII) is accompanied by a similar ring enlargement, thus :

Me OH | Me | :C:CH
Me |
AcO
(LV.)
→
Me | Me | OH | :O
Me |
HO
(LVI.)
→

(LVII.)
Me Me | Me | 17a :O
HO
Me Me | Me | OH
HO
(LVIII.)
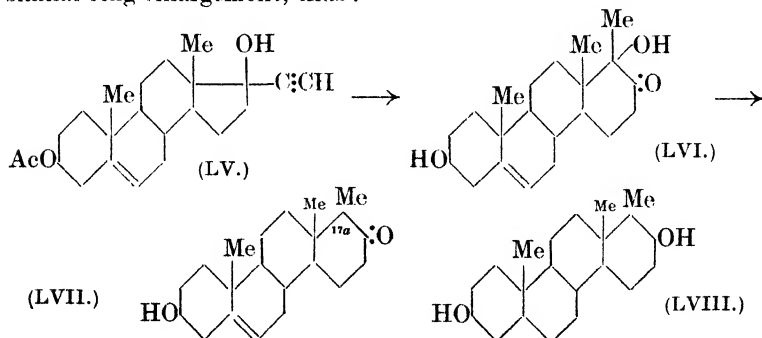
[68] *Ber.*, 1939, **72**, 1119.   [69] *Helv. Chim. Acta*, 1939, **22**, 626.
[70] H. E. Stavely, *J. Amer. Chem. Soc.*, 1939, **61**, 79; L. Ruzicka and F. Hunziger, *Helv. Chim. Acta*, 1939, **22**, 707; L. Ruzicka and H. F. Meldahl, *ibid.*, 1940, **23**, 513.

Again, it follows that a similar ring enlargement occurs in the Miescher–Kägi partial synthesis of *neo*pregnenolone, which is now named 3(β)-hydroxy-17a-methyl-Δ⁵-*D*-homoandrosten-17-one. Additional support for the correctness of these formulations was supplied by L. Ruzicka and H. F. Meldahl,[71] who reduced (LVII) to the saturated diol (LVIII), which on dehydrogenation with selenium gave 1-methylchrysene.[72] A remarkable partial synthesis of *D*-homoandrostane derivatives has been accomplished by M. W. Goldberg and R. Monnier,[73] using the ring enlargement method of M. Tiffeneau.[74] Reduction of the cyanohydrin of dehydroandrosterone (LIX) yielded the hydroxy-amine (LX), which on treatment with nitrous acid suffered ring enlargement with formation of 3(β)-hydroxy-*D*-homoandrostan-17a-one (LXI), the structure of which was confirmed by treatment with methylmagnesium iodide and dehydrogenation of the product, 1-methylchrysene then being obtained.
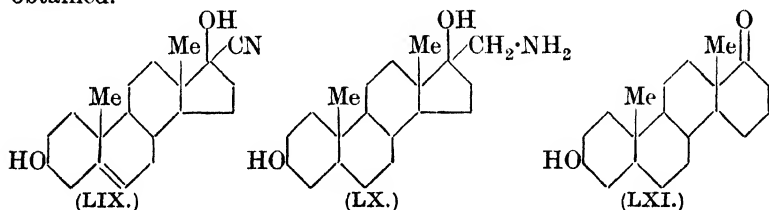
The hydration of (LV) has been reinvestigated by H. E. Stavely.[75] Using the boron trifluoride–mercuric oxide catalyst in the presence of aniline,[76] he obtained the anil (LXII), hydrolysis of which (alkali being excluded) gave 17-hydroxy-Δ⁵-*iso*pregnenolone (LXIII, R = H), the structure of which was established by oxidation of its 3-monoacetate (LXIII, R = Ac) (the ethenoid linkage being protected by bromine) to dehydroandrosterone acetate. Treatment of
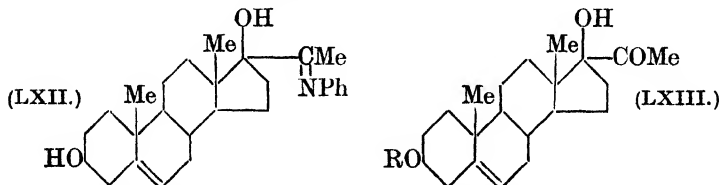
(LXIII) with alkali causes ring enlargement with formation of (LVI). Rearrangement of compounds of type (LXIII) to *D*-homo-

[71] *Helv. Chim. Acta*, 1940, **23**, 364, 513.

[72] L. Ruzicka and R. Marcus, *ibid.*, p. 385.   [73] *Ibid.*, p. 376.

[74] M. Tiffeneau, P. Weill, and D. Tchoubar, *Compt. rend.*, 1937, **205**, 54.

[75] *J. Amer. Chem. Soc.*, 1940, **62**, 489.

[76] Compare M. W. Goldberg and R. Aeschbacher, *Helv. Chim. Acta*, 1939, **22**, 1188.

androstane derivatives is controlled by the orientation of the 17-hydroxyl group; when this has the α-configuration, ring enlargement occurs on treatment with alkali, but this is not so when the β-configuration pertains, as in many adrenal steroids.

Sapogenins.

During the last two years the steroid sapogenins (neutral sapogenins) have been a focal point of interest in steroid chemistry; this is largely due to the versatile and prolific researches of R. E. Marker and his collaborators, which have brought to light a hitherto unsuspected reactivity of the sapogenin side chain whereby these plant products now become a source of the animal hormones progesterone, deoxycorticosterone, and testosterone.

Sarsasapogenin, Smilagenin, Tigogenin, and neo*Tigogenin.*—The side chain of the neutral sapogenins was formulated as in (I) by R. Tschesche and A. Hagedorn,[77] who assigned this structure to tigogenin, rings *A* and *B* having the cholestane configuration. S. N. Farmer and G. A. R. Kon [78] showed that oxidation of sarsasapogenin acetate with chromic acid gives the acetate of a lactone formulated as (II); this was converted into ætiobilianic acid (III), thus showing that sarsasapogenin is a coprostane derivative and that the only possible points of attachment for the side chain are C_{16} and C_{17}. By this method tigogenin had previously [77] been degraded to ætio*allo*bilianic acid, which differs from (III) in the orientation around C_5. That the hydroxyl group of sarsasapogenin is located
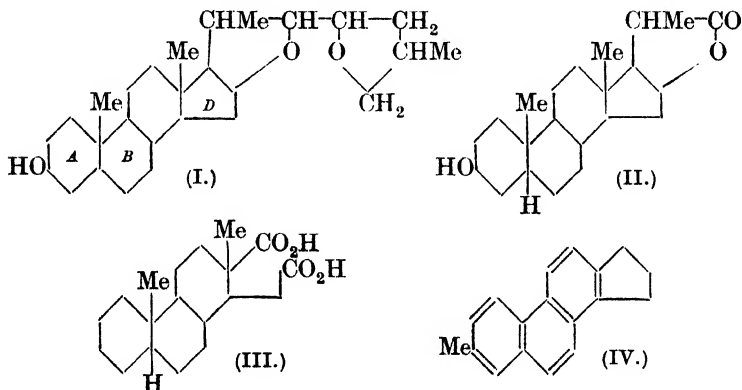
at C_3 was indicated by surface film measurements, by the observation that sarsasapogenin is precipitated by digitonin,[78, 79] and established by the dehydrogenation of methyl sarsasapogenin (prepared by the

[77] *Ber.*, 1935, **68**, 1412, 2247; 1936, **69**, 797.   [78] *J.*, 1937, 414.
[79] F. A. Askew, S. N. Farmer, and G. A. R. Kon, *J.*, 1936, 1399.

action of methylmagnesium iodide on sarsasapogenone), the hydro-
carbon (IV) being obtained, the structure of which was established
by synthesis.[80]

The oxidation of sarsasapogenin acetate has also been investigated
by L. F. Fieser and R. P. Jacobsen,[81] who isolated the C_{22}-lactone
(II), and in addition an acid, sarsasapogenoic acid, $C_{27}H_{42}O_5$,
analogous to the tigogenoic acid obtained by R. Tschesche and
A. Hagedorn [77] by a similar oxidation of tigogenin acetate. Fieser
and Jacobsen concluded that sarsasapogenoic acid is represented by
(V) (a formulation suggested by Tschesche and Hagedorn [77] for
tigogenoic acid), which explains the facile conversion of (V) by
treatment with alkali into a hydroxy-$\alpha\beta$-unsaturated keto-acid,
anhydrosarsasapogenoic acid (VI), all the functional groups of which
have been characterised.[82] Reduction of (VI) gave a tetrahydro-

anhydrosarsasapogenoic acid (VII), which readily yielded an
acetate-lactone (VIII). The authors concluded that the only
formulation for the side chain of sarsasapogenin consistent with this
series of transformations is (I).
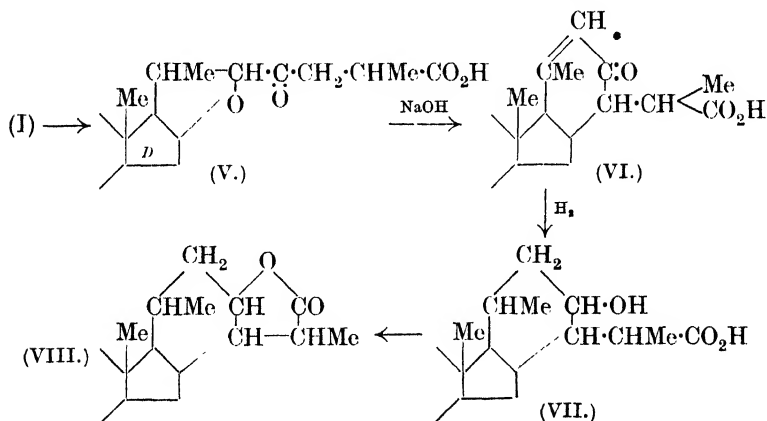
The oxidation of sarsasapogenin acetate with chromic anhydride
was also examined by R. E. Marker and E. Rohrmann,[83] who
isolated the C_{22}-lactone (II), sarsasapogenoic acid, and a keto-acid,
$C_{22}H_{34}O_4$, to which is ascribed the structure (IX), since on reduction
it gives the C_{22}-lactone (II). The latter has been used in an in-
genious manner to demonstrate [84] that sarsasapogenin differs from

[80] G. A. R. Kon and A. M. Woolman, *J.*, 1939, 794.

[81] *J. Amer. Chem. Soc.*, 1938, **60**, 28, 2753.

[82] L. F. Fieser and R. N. Jones, *ibid.*, 1939, **61**, 532; L. F. Fieser, E. M.
Fry, and R. N. Jones, *ibid.*, p. 1849.

[83] *Ibid.*, p. 1285.   [84] R. E. Marker and E. Rohrmann, *ibid.*, p. 1291.

tigogenin in the orientation around C_5, and incidentally to confirm the location of the hydroxyl group of sarsasapogenin. Oxidation of the C_{22}-lactone yielded the corresponding ketone (X), bromination of which, followed by elimination of hydrogen bromide, gave the αβ-unsaturated keto-lactone (XI), which on reduction with sodium and alcohol gave a C_{22}-lactone (XII) identical with that previously obtained by R. Tschesche and A. Hagedorn [77] directly from tigogenin.

CHMe·CO₂H (IX.) → (II) → CHMe—CO (X.) →

(XI.) → (XII.)
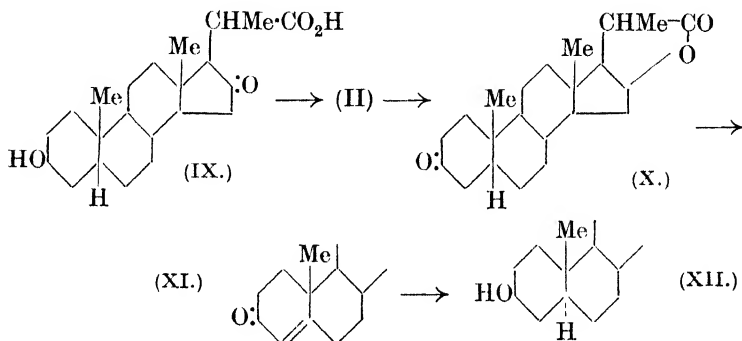
Further proof that sarsasapogenin is a 3(β)-hydroxycoprostane derivative was supplied by R. E. Marker and E. Rohrmann,[85] who converted the genin into 3(β)-hydroxyætiocholan-17-one [86] and thence into testosterone.

A consideration of the reactivity of the side chain of sarsasapogenin led R. E. Marker and E. Rohrmann [87] to suggest the alternative side-chain formulation (XIII), which is based upon the reactivity of the side-chain oxygen atoms in acid media, no such reactivity being observed in neutral or alkaline media. Sarsasapogenin is isomerised by hydrochloric acid to *iso*sarsasapogenin, which has been shown to be identical with the naturally occurring smilagenin.[78, 79, 88] Sarsasapogenone is likewise isomerised by acids.[87, 81] Again, sarsasapogenin acetate readily gives a (side-chain) bromoderivative [87, 89] which on treatment with sodium and alcohol regenerates the genin. Sarsasapogenin also reacts with alkylmagnesium halides to give products which contain two esterifiable hydroxyl groups.[85] The authors conclude that sarsasapogenin contains a protected (ketal) carbonyl group (XIII) and the acid

[85] *J. Amer. Chem. Soc.*, 1940, **62**, 900.
[86] L. Ruzicka, M. W. Goldberg, J. Meyer, H. Brüngger, and E. Eichenberger, *Helv. Chim. Acta*, 1935, **17**, 1395.
[87] *J. Amer. Chem. Soc.*, 1939, **61**, 846.
[88] G. A. R. Kon, H. R. Soper, and A. M. Woolman, *J.*, 1939, 1201.
[89] R. E. Marker and E. Rohrmann, *J. Amer. Chem. Soc.*, 1939, **61**, 1921.

isomerisation is represented as a side-chain rearrangement of
(XIII) ⟶ (XIV).

(XIII.)   (XIV.)

(XV.)
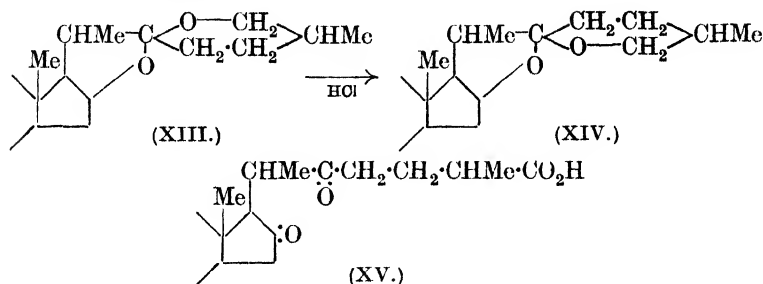
A re-examination of sarsasapogenoic acid led R. E. Marker and
E. Rohrmann [90] to formulate this acid as a hydroxy-diketo-mono-
carboxylic acid (XV). A further point advanced in favour of the
ketal side-chain structure (XIII) or (XIV) for the sapogenins is the
observation [77] that oxidation of digitogenin and of gitogenin gives
methylsuccinic and α-methylglutaric acids. The formation of the
latter had previously to be attributed to the nucleus.

The further investigation of the acid isomerisation of the neutral
sapogenins together with the application of a method for the con-
version of a 3-hydroxycoprostane derivative into the corresponding
3(β)-hydroxycholestane derivative led to the establishment of the
relationships between tigogenin, neotigogenin, sarsasapogenin, and
smilagenin.[91] Oxidation of sarsasapogenin to the corresponding
C_3-ketone, sarsasapogenone, followed by bromination of the latter,
gives a dibromo-ketone, one halogen atom being attached to C_4 and
the other to the side chain. Treatment of this with pyridine yields
a bromo-Δ⁴-dehydrosarsasapogenone, reduction of which with
sodium and alcohol effects replacement of the side-chain bromine
atom by hydrogen and addition of four hydrogens to the αβ-unsatur-
ated ketone group. The product proved to be identical with neo-

Sarsasapogenone.   (+ 1 Br in side   (+ 1 Br in side   neo-
                       chain)   chain)   Tigogenin.
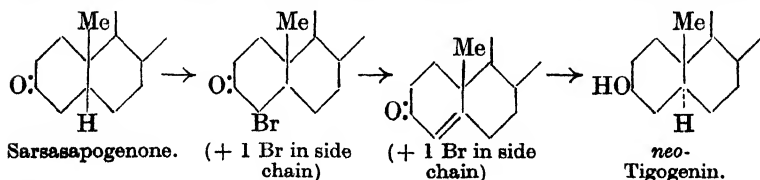
tigogenin, a sapogenin isolated by L. H. Goodson and C. R. Noller [92]
from *Chlorogalum pomeridianum*. In exactly the same way smila-

    [90] *J. Amer. Chem. Soc.*, 1939, **61**, 2072, 3477.
    [91] R. E. Marker and E. Rohrmann, *ibid.*, 1940, **62**, 647; R. E. Marker,
E. Rohrmann, and E. M. Jones, *ibid.*, p. 1162.
    [92] *Ibid.*, 1939, **61**, 2420.

genin was converted into tigogenin and, as expected, treatment of *neo*tigogenin with mineral acid yielded tigogenin, thus showing that this pair of sapogenins is related in the same way as sarsasapogenin and smilagenin. Sarsasapogenin and *neo*tigogenin have the " normal " side-chain structure and differ from one another in the configuration of C_5; smilagenin and tigogenin have the " *iso* "- side-chain structure and likewise differ in the orientation around C_5.

The Conversion of Neutral Sapogenins into Pregnane Derivatives.— ψ-*Sapogenins.* Late in 1939 it was shown by R. E. Marker and E. Rohrmann [93] that, when a sapogenin is heated to 200° with acetic anhydride, it is isomerised to a ψ-sapogenin, which on mild oxidation yields a pregnane derivative. Thus sarsasapogenin (XIII) [93] and smilagenin (*iso*sarsasapogenin) (XIV),[94] when heated with acetic anhydride (followed by hydrolysis), give the same ψ-sarsasapogenin (XVI),[95] which when mildly oxidised gives Δ^{16}-pregnen-3 : 20-dione (XVII) [96] together with a small quantity of 3-ketoætiobilianic acid. In the same way tigogenin gives ψ-tigogenin [97] and thence Δ^{16}-*allo*-pregnen-3 : 20-dione.[96] That the hydroxyl group in tigogenin has the β-configuration is also confirmed by a similar conversion of the genin into 3(β)-hydroxy*allo*pregnan-20-one.

R. E. Marker and his collaborators conclude that the available evidence indicates that the ψ-genins are oxygenated at C_{22} and contain a C_{16}–C_{17} ethylenic linkage.[98] The ψ-genins have been formulated as (XVI) and, although evidence has been adduced in favour of this formulation,[99] it cannot be considered to be rigidly established.

(XIII) $\longrightarrow$ (XIV)

Me OH
C=C·CH₂·CH₂·CHMe·CH₂·OH
Me

(XVI.)

$\longrightarrow$

COMe
Me
Me
O:
H   (XVII.)
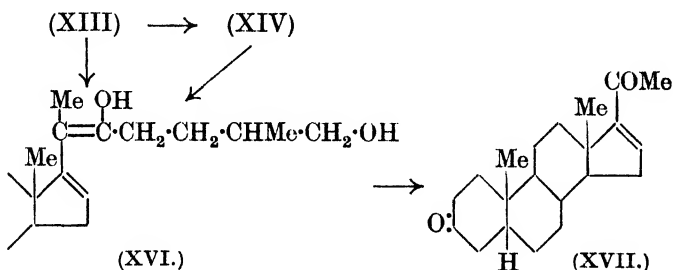
The isomerisation of sarsasapogenin into ψ-sarsasapogenin is reversible; on treatment with mineral acids under mild conditions,

[93] *J. Amer. Chem. Soc.*, 1939, **61**, 3592; 1940, **62**, 518.

[94] R. E. Marker, E. Rohrmann, and E. M. Jones, *ibid.*, 1940, **62**, 648.

[95] R. E. Marker and E. Rohrmann, *ibid.*, p. 521.

[96] *Ber.*, 1939, **72**, 1614.

[97] R. E. Marker and E. Rohrmann, *J. Amer. Chem. Soc.*, 1940, **62**, 898.

[98] *Idem, ibid.*, p. 896.

[99] R. E. Marker, E. M. Jones, and J. Kreuger, *ibid.*, p. 2532.

the ψ-genin regenerates sarsasapogenin.[98] Thus the ψ-genin of the coprostane configuration re-forms the " normal " genin side chain. On the other hand, ψ-tigogenin reacts with mineral acids to give tigogenin and not *neo*tigogenin; in this case the ψ-genin of the cholestane configuration re-forms the " *iso* "-genin side chain.

The ease of conversion of a sapogenin into a pregnane derivative has been further demonstrated by R. E. Marker, E. Rohrmann, H. M. Crooks, E. L. Wittle, E. M. Jones, and D. L. Turner.[1] Oxidation of sarsasapogenin acetate with potassium persulphate, followed by hydrolysis, gave $3 : 16 : 20$-trihydroxypregnane, the reaction being formulated as follows :
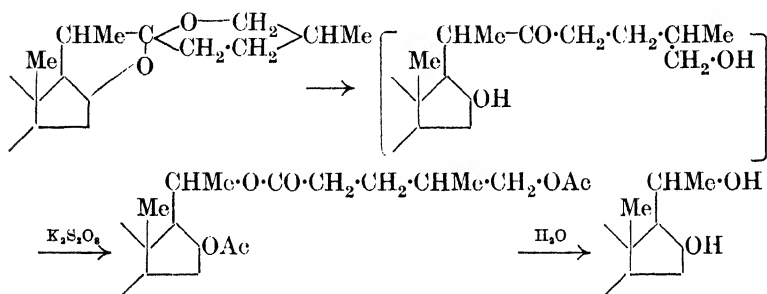
Sarsasapogenin has been converted into testosterone by a modification of this reaction ;[2] Δ^{16}-pregnenedione (XVII) (obtained from sarsasapogenin) was reduced to pregnane-$3 : 20$-dione (XVIII), the 4-bromo-derivative of which (XIX)[3] was oxidised with persulphuric acid to yield (XX), which on treatment with pyridine, followed by hydrolysis, gave testosterone (XXI) in small yield.
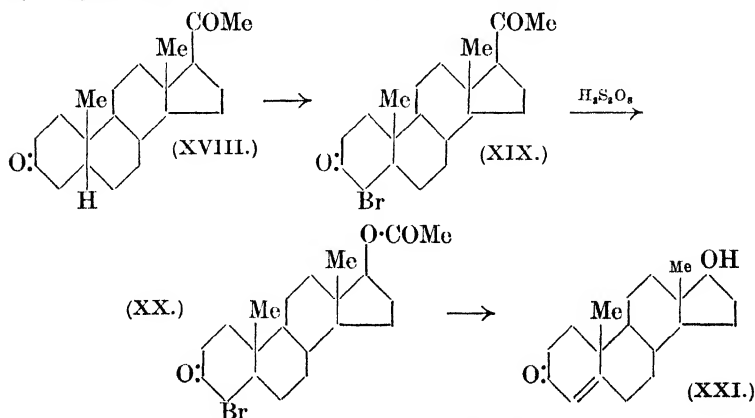
[1] *J. Amer. Chem. Soc.*, 1940, **62**, 525.   [2] R. E. Marker, *ibid.*, p. 2543.
[3] A. Butenandt and J. Schmidt, *Ber.*, 1934, **67**, 1901.

Diosgenin.—Diosgenin was isolated by T. Tsukamoto, Y. Ueno, and T. Ota [4] from the *Dioscorea* and characterised as an unsaturated neutral sapogenin.[5] It was later isolated from the rhizomes of *Trillium erectum* [6] and *Aletris farinosa* (L).[7] A comparison of the constants of dihydrodiosgenin and tigogenin led
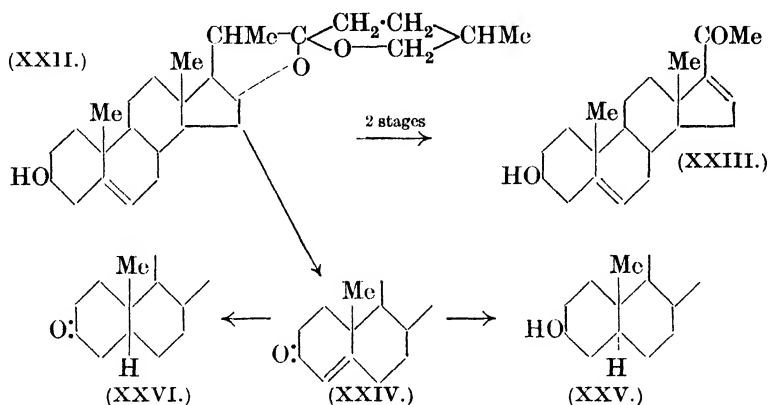
R. E. Marker and E. Rohrmann [8] to suggest that diosgenin is a dehydrotigogenin, a suggestion substantiated by later investigations. Diosgenin was shown [9] to have the structure (XXII); ψ-diosgenin on oxidation (the 3-hydroxyl group and the Δ^5-linkage being protected in the usual manner) yields 3-hydroxy-$\Delta^{5:16}$-pregnadien-20-one (XXIII) and thence progesterone. Oxidation (Oppenauer) of diosgenin gives Δ^4-tigogenone * (XXIV), reduction of which (*a*) with sodium and alcohol gave tigogenin (XXV) and (*b*) with a palladium catalyst gave smilagenone (XXVI). More recently R. E. Marker [10] has converted diosgenin into dihydroandrosterone.

Chlorogenin.—From the rhizomes of *Chlorogalum pomeridianum* P. Liang and C. R. Noller [11] isolated, in addition to tigogenin, a new sapogenin, chlorogenin, $C_{27}H_{44}O_4$; from the same source, gitogenin [12]

[4] *J. Pharm. Soc. Japan*, 1936, **56**, 135; 1937, **57**, 9.

[5] T. Tsukamoto, Y. Ueno, T. Ota, and R. Tschesche, *ibid.*, 1937, **57**, 283.

[6] R. E. Marker, D. L. Turner, and P. R. Ulshafer, *J. Amer. Chem. Soc.*, 1940, **62**, 2542; R. E. Marker and J. Krueger, *ibid.*, p. 2548.

[7] R. E. Marker, *ibid.*, p. 2620.

[8] *Ibid.*, 1939, **61**, 1516.

[9] R. E. Marker, T. Tsukamoto, and D. L. Turner, *ibid.*, 1940, **62**, 2525.

[10] R. E. Marker, *ibid.*, p. 2621.

[11] *Ibid.*, 1935, **57**, 525.

[12] C. R. Noller, L. H. Goodson, and M. Synerholm, *ibid.*, 1939, **61**, 1707.

* The nomenclature is confusing; this derivative would be better named Δ^4-diosgenone to differentiate it from tigogenone, which is a *saturated* ketone.

and *neo*tigogenin [13] have subsequently been isolated.   C. R. Noller [14] provisionally formulated chlorogenin as a 3(α) : 12-dihydroxy-sapogenin.   R. E. Marker and E. Rohrmann [15] showed that the genin gives a digitonide (see, however, the comments of C. R. Noller [16] on digitonide formation) and that on oxidation it gives a diketone, chlorogenone, which yields a pyridazine derivative; on this evidence Marker and Rohrmann suggested that chlorogenin is a 3(β) : 6-dihydroxy-steroid derivative.   The characterisation of a 3 : 6-diketone by the formation of a " pyridazine " derivative has been criticised by C. R. Noller.[17]

R. E. Marker, E. M. Jones, and D. L. Turner [18] have confirmed the 3 : 6-dihydroxycholestane structure for chlorogenin by the conversion of diosgenin into chlorogenone by the following route :

Me　　　　　　　　　Me　　　　　　　　　Me

HO　　　$\xrightarrow{CrO_3}$　　　O:　　　$\xrightarrow{Zn + AcOH}$　　　O:

O　　　　　　　　H O

Diosgenin　　　　　　　　　　　　　　　Chlorogenone

These reactions are comparable with the conversion of cholesterol into 3 : 6-diketo-Δ^4-cholestene,[19] and of the latter into 3 : 6-diketo-cholestane.[20]

Sterols.

Oxidation of Cholesterol.—In addition to dehydroandrosterone and acidic products, oxidation of cholesterol (as acetate dibromide) yields 3(β)-hydroxy-Δ^5-norcholesten-25-one (I),[21] a hydroxy-lactone to which has been ascribed a structure of the type (II),[22] Δ^5-pregnen-olone,[23] and the unsaturated keto-alcohol (III) ; [24] in the formation of the last, the removal of the group originally attached to C_{13} is probably to be ascribed to a post-oxidative change (cf. the oxidation of β-ergostenol).[25]   Partial removal of the sterol side chain with formation of neutral products has also been achieved in the case of

[13] L. H. Goodson and C. R. Noller, *J. Amer. Chem. Soc.*, 1939, **61**, 2420.

[14] *Ibid.*, 1937, **59**, 1092; 1938, **60**, 1629.

[15] *Ibid.*, 1939, **61**, 946.　　　　　[16] *Ibid.*, p. 2717.

[17] *Ibid.*, p. 2976.　　　　　[18] *Ibid.*, 1940, **62**, 2537.

[19] H. Mauthner and W. Suida, *Monatsh.*, 1896, **17**, 579; A. Windaus, *Ber.*, 1907, **40**, 257.

[20] A. Windaus, *Ber.*, 1903, **36**, 3755; 1906, **39**, 2252.

[21] L. Ruzicka and W. H. Fischer, *Helv. Chim. Acta*, 1937, **20**, 1291; J. Hattori, *J. Pharm. Soc. Japan*, 1938, **58**, 150.

[22] K. Miescher and W. H. Fischer, *Helv. Chim. Acta*, 1939, **22**, 155.

[23] K. Fujii and T. Matsukawa, *J. Pharm. Soc. Japan*, 1936, **56**, 24.

[24] H. Köster and W. Logemann, *Ber.*, 1940, **73**, 298.

[25] T. Achtermann, *Z. physiol. Chem.*, 1934, **225**, 141.

*epi*cholestanol (as acetate), oxidation of which gives androsterone together with the aldehyde (lV). At a lower reaction temperature, the hydroxy-ketone (V) is obtained in relatively high yield, the formation of androsterone being suppressed.[26] The previously reported oxidation of 5 : 6-dibromocholestanone to progesterone [27] could not be repeated by M. A. Spielman and R. K. Meyer,[28] who, however, obtained a 0·2% yield of progesterone by oxidation of cholesterol dibromide.

O. Rosenheim and W. W. Starling[29] showed that oxidation of cholesterol with selenium dioxide gives *cis*-3 : 4-dihydroxy-Δ^5-cholestene;

$$\text{CHMe} \cdot [\text{CH}_2]_3 \cdot \text{COMe}$$

(I.)

$$\text{CHMe} \cdot [\text{CH}_2]_3 \cdot \text{COMe}$$

(II.)

(III.)

$$\text{CHMe} \cdot [\text{CH}_2]_2 \cdot \text{CHO}$$

(IV.)

$$\text{CHMe} \cdot [\text{CH}_2]_3 \cdot \text{COMe}$$

(V.)
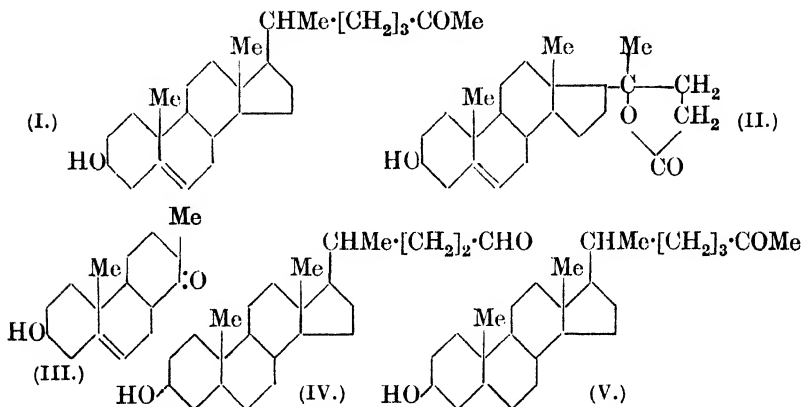
oxidation of cholesteryl esters with the same reagent gives monoesters of the *cis*-3 : 4-diol,[29, 30] together with esters of 3 : 6-dihydroxy-Δ^4-cholestene.[29, 31] Monoesters of the *cis*-3 : 4-diol have also been obtained by the action of potassium acetate on cholesteryl acetate dibromide [32] and by the action of the same reagent on 6-chloro-3-benzoyloxy-Δ^4-cholestene.[33] In contradistinction to the *cis*-3 : 4-diol, it has been shown by F. S. Spring and G. Swain [33] that the 4-monoesters do not give insoluble digitonides in spite of the presence of a 3(β)-hydroxyl group.

At various times four different substances have been allocated

[26] L. Ruzicka, M. Oberlin, H. Wirz, and J. Meyer, *Helv. Chim. Acta*, 1937, **20**, 1283; M. I. Ouchakov, P. F. Epifanski, and A. D. Tshinaeva, *Bull. Soc. chim.*, 1937, **4**, 1390.

[27] N. I. Tavastsherna, *Arch. Sci. biol.*, 1936, **40**, 141.

[28] *J. Amer. Chem. Soc.*, 1939, **61**, 893.

[29] *J.*, 1937, 377.

[30] R. E. Marker and E. Rohrmann, *J. Amer. Chem. Soc.*, 1939, **61**, 3022.

[31] A. Butenandt, and E. Hausmann, *Ber.*, 1937, **70**, 1154.

[32] V. A. Petrow, *J.*, 1937, 1077.

[33] F. S. Spring and G. Swain, *J.*, 1939, 1356; *Nature*, 1940, **146**, 718.

the 3: 6-dihydroxy-Δ^4-cholestene structure (IX). T. Westphalen[34] prepared an unsaturated diol (as diacetate) by the dehydration of the diacetate of cholestanetriol-I with sulphuric acid–acetic anhydride. H. Lettré and M. Müller[35] showed that this cannot be a 3 : 6-Δ^4-unsaturated diol, since on oxidation it gives neither 3 : 6-diketo-Δ^4-cholestene nor 3 : 6-diketocholestane; they suggested that the dehydration is accompanied by a retropinacolinic rearrangement, a suggestion receiving support from experiments of V. A. Petrow, O. Rosenheim, and W. W. Starling.[36] The structure (VI) ascribed to the diol by these authors is compatible with the behaviour of the diol on oxidation.[37]

By treatment of 5-chloro-3 : 6-dibenzoyloxycholestane (VII, R = COPh) with quinoline, followed by hydrolysis, H. Lettré and M. Müller[35] obtained a product which they described as 3 : 6-dihydroxy-Δ^4-cholestene. This formulation has been shown to be
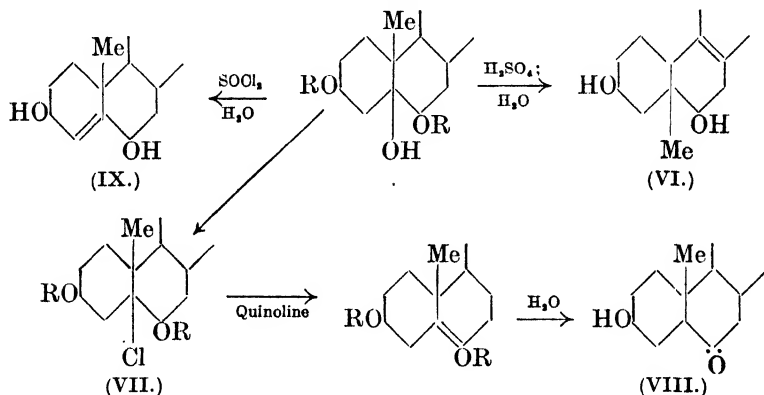
erroneous by V. A. Petrow, O. Rosenheim, and W. W. Starling,[36] who found that this " diol " is 6-ketocholestanol (VIII). 3 : 6-Dihydroxy-Δ^4-cholestene (IX) was obtained by I. M. Heilbron, E. R. H. Jones, and F. S. Spring[38] by partial reduction of 6-keto-3-acetoxy-Δ^4-cholestene; the constitution of the latter was established by its conversion into 3 : 6-diketocholestane. This diol probably differs from the isomeric diol (IX), obtained either by oxidation of cholessteryl esters with selenium dioxide[29, 31] or by dehydration of the diester of the triol-I by means of thionyl chloride,[36] in the orientation around C_6. The stereochemical relationship of the two isomeric 3(β) : 5 : 6-trihydroxycholestanes (triols-I and -II) has been examined

[34] Ber., 1915, **48**, 1064; J. L. Dunn, I. M. Heilbron, R. H. Phipers, K. M. Samant, and F. S. Spring, J., 1934, 1580; V. A. Petrow, J., 1937, 1077.
[35] Ber., 1937, **70**, 1947.   [36] J., 1938, 677.
[37] V. A. Petrow, J., 1939, 998.   [38] J., 1937, 801.

by B. Ellis and V. A. Petrow.[39]   Triol-I, which is obtained by oxid-
ation of cholesterol with hydrogen peroxide or by hydrolysis of
α-cholesterol oxide,[40, 32] has been shown by R. Criegee [41] to be a
trans-α-glycol $(C_5–C_6)$.   Triol-II is prepared by the oxidation of
cholesterol with either potassium permanganate [42] or osmic acid [43]
and, as is to be expected from its method of preparation, is a *cis*-α-
glycol.[41]   Since oxidation of the isomeric triols yields different
5-hydroxy-3 : 6-diketocholestanes,[42] it follows that the two triols
differ only in orientation around C_5.   Ellis and Petrow have now
shown that the 3-keto-5 : 6-diol monoacetate (XI) derived from the
6-monoacetate (X) of triol-I gives a 2-bromo-derivative which with
alkali yields a *trans*-annular oxide (XII).   The alternative mechan-
ism whereby the bromine atom is introduced at C_4 to yield a $C_4–C_5$
oxide is excluded because of the stability of the oxide obtained.
Oxidation of the 6-monoacetate (X) of triol-I gives the lactonic acid

(XI.)   →   →   (XII.)

(X.)   →   (XIII.)   →   (XIV.)

(XV.)   (XVI.)
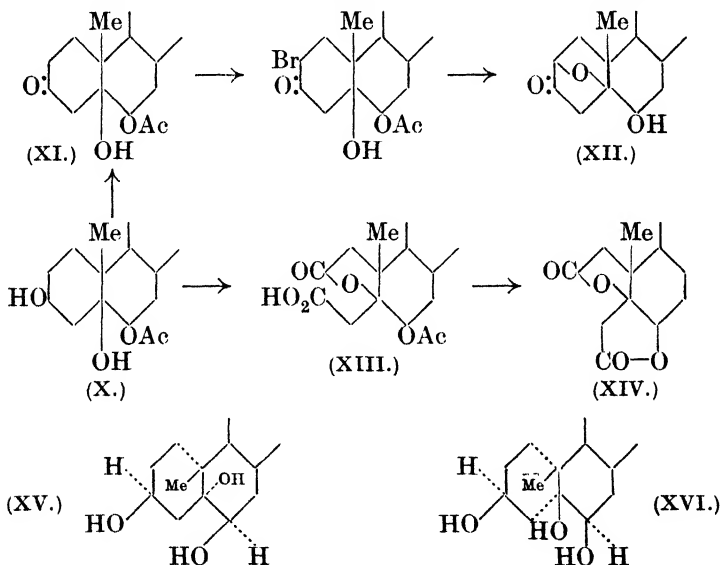
(XIII), hydrolysis of which gives the dilactone (XIV).   Thus
bromination of the 3-ketone (XI) gives a 2-bromo-derivative and

[39] *J.*, 1939, 1078.
[40] R. H. Pickard and J. Yates, *J.*, 1908, **93**, 1678; T. Westphalen, *Ber.*, 1915, **48**, 1064.
[41] *Ber.*, 1932, **65**, 1770.
[42] A. Windaus, *Ber.*, 1907, **40**, 259; see also R. E. Marker and E. Rohrmann, *J. Amer. Chem. Soc.*, 1940, **62**, 516.
[43] M. I. Ushakow and A. I. Lieutenberg, *Nature*, 1937, **140**, 466; *J. Gen. Chem. Russia*, 1939, **9**, 69.

oxidation leads to $C_2\|C_3$ rupture, a behaviour known to be characteristic of C_3-keto-steroids in which rings A and B are *trans*-fused.[44] Ellis and Petrow conclude that this orientation pertains in the 3-keto-5 : 6-diol monoacetate and consequently in the parent triol-I, which is therefore represented by (XV) and triol-II by (XVI). Unfortunately these decisions are dependent upon the assumption that the course of bromination and oxidation of saturated 3-keto-steroids is not altered by the replacement of the C_5-hydrogen by a hydroxyl group.*

Sulphonation of Steroid Ketones.—The sulphonation of a series of steroid ketones has been studied by A. Windaus,[46] one object of the study being to sulphonate the methyl group attached to C_{10}; this type of sulphonation has not been observed. Sulphonation of 3-keto-Δ^4-cholestene gives the corresponding 6-sulphonic acid (XVII), which is soluble in water; its sodium salt yields water-soluble complexes with cholesterol, cholestene, 3-keto-Δ^4-cholestene, vitamin-D, methylcholanthrene and benzpyrene. Sulphonation of cholestanone gives the 2-sulphonic acid and sulphonation of coprostanone gives a mixture of the 2- (XVIII) and the 4-sulphonic acid. The formation of the former is surprising in view of the tendency for

(XVII.)   (XVIII.)   (XIX.)
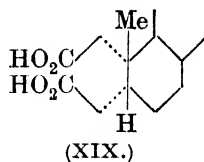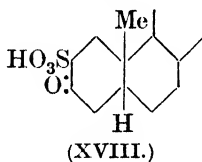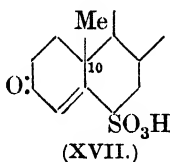
coprostanone to brominate in the 4-position and to suffer $C_3\|C_4$ oxidation. Oxidation of coprostanone-2-sulphonic acid gives the hitherto unknown dicarboxylic acid (XIX).†

    [44] A. Butenandt and A. Wolff, *Ber.*, 1935, **68**, 2091.
    [45] *J. Org. Chem.*, 1939, **4**, 506.
    [46] A. Windaus and E. Kuhr, *Annalen*, 1937, **532**, 52; A. Windaus and K. H. Mielke, *ibid.*, 1938, **536**, 116; E. Kuhr, *Ber.*, 1939, **72**, 929.
    [47] R. E. Marker, E. L. Wittle, L. Plambeck, E. Rohrmann, J. Krueger, and P. R. Ulshafer, *J. Amer. Chem. Soc.*, 1939, **61**, 3317.

    * The configurations (XV) and (XVI) adopted for triols-I and -II, respectively, appear to be independent of the assumption made by Ellis and Petrow. First, the immediate lactonisation of the (not isolated) $C_2\|C_3$ dicarboxylic acid to the lactonic acid (XIII) and of the (not isolated) hydroxy-lactone-acid to the dilactone (XIV) requires that rings A and B in triol-I be *trans*-fused. Secondly, the oft-observed fact that *cis*-hydroxylation of 3(β)-hydroxy-Δ^5-steroids by means of osmic acid is inhibited by acetylation finds an explanation if triol-II is represented by (XVI) (cf. M. Ehrenstein).[45]

    † A serious confusion between the dicarboxylic acids derived from cholestanol and coprostanol has arisen in the literature. R. E. Marker *et al.*[47] claim that the dicarboxylic acid, m. p. 247°, obtained by oxidation of copro-

Photoisomers of Ergosterol and Related Sterols.—The four stereo-isomers ergosterol, lumisterol, pyrovitamin-D_2 (pyrocalciferol) and *iso*pyrovitamin-D_2 (*iso*pyrocalciferol) have been further correlated by T. Kennedy and F. S. Spring,[51] who find that the acetate of pyrovitamin-D_2, like ergosterol and unlike lumisterol and *iso*-pyrovitamin-D_2 acetate, yields a bimolecular oxidation product—" pinacol diacetate "—pyrolysis of which yields *neo*ergosteryl acetate. The " pinacol " of dehydroergosterol has been examined by T. Ando [52] and by A. Windaus and C. Roosen-Runge,[53] the conclusion being that it has the structure (XX).

Following upon the isolation of vitamin-D_4 (obtained by irradiation of 22-dihydroergosterol) [54] A. Windaus and B. Güntzel [55] have isolated the intermediate photoisomers lumisterol$_4$ and tachysterol$_4$. The pyrolysis of vitamin-D_3 has been investigated by A. Windaus, M. Deppe, and C. Roosen-Runge,[56] who find that, as in the case of vitamin-D_2, a mixture of two isomers is formed. These two isomers, pyrovitamin-D_3 and *iso*pyrovitamin-D_3, together with 7-dehydrocholesterol and lumisterol$_3$ represent the four stereoisomers of structure (XXI) differing in orientation around C_9 and C_{10}. The

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stanol or coprostanone,[48] is the $C_2||C_3$-diacid (XIX) on the grounds that A. Windaus and T. Riemann [49] further oxidised the dibasic acid to the tribasic *iso*lithobilianic acid (which without doubt is a $C_2||C_3$ acid). The structure ascribed by R. E. Marker *et al.* to the dicarboxylic acid from coprostanone is incorrect, since this acid gives the same pyroketone as is obtained from dihydro-Diels acid, thus showing that the two acids must be stereoisomers differing in the orientation of an asymmetric centre in the α-position to one carboxyl group, *i.e.*, they are $C_3||C_4$-dibasic acids differing in orientation around C_5.[50] Concerning the Windaus–Riemann transformation of the coprostane diacid into *iso*lithobilianic acid, A. Windaus [50] says that this " scheint unrichtig zu sein."

The new coprostanedicarboxylic acid obtained by R. E. Marker *et al.* by the oxidation of " coprostanediol-3 : 4 " and formulated as a $C_3||C_4$-diacid may be identical with the coprostane $C_2||C_3$-diacid obtained by A. Windaus and K. H. Mielke [46] and mentioned above. It is possible that during the preparation of the coprostanediol from 4-bromocoprostanone, migration from C_4 to C_3 has occurred and that the coprostane-3 : 4-diol is in reality a coprostane-2 : 3-diol.

The conclusion of R. E. Marker *et al.* that " The greater part of the oxidative fission of 3-substituted derivatives of the coprostane configuration (except those of the bile acid series) takes place at the 2, 3 bond rather than at the 3, 4 bond as has been generally assumed," is not sound.

[46] J. A. Gardner and W. Godden, *Biochem. J.*, 1913, **7**, 588; A. Windaus, *Ber.*, 1916, **49**, 1724.

[49] *Z. physiol. Chem.*, 1923, **126**, 277.   [50] A. Windaus, *ibid.*, 1932, **213**, 185.
[51] *J.*, 1939, 250.   [52] *Bull. Chem. Soc. Japan*, 1939, **14**, 482.
[53] *Ber.*, 1940, **73**, 321.
[54] A. Windaus and G. Trautmann, *Z. physiol. Chem.*, 1937, **247**, 185.
[55] *Annalen*, 1939, **538**, 120.   [56] *Ibid.*, 1939, **537**, 1.

stereorelationships of these isomers were established in the same way as in the case of the corresponding ergosterol derivatives.

(XX.)   (XXI.)
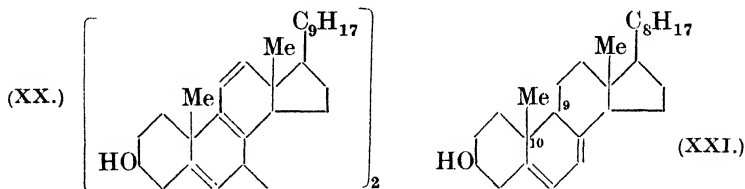
7-Dehydro*epi*cholesterol [3(α)-hydroxy-$\Delta^{5:7}$-cholestadiene] has been prepared by A. Windaus and J. Naggatz.[57] Although the changes in the absorption spectrum during irradiation with ultra-violet light show that this compound suffers the same type of chemical transformations, the product has only one-tenth the antirachitic activity of a similar product from 7-dehydrocholesterol [3(β)-hydroxy-$\Delta^{5:7}$-cholestadiene]. Photopyrocalciferol and photo*iso*-pyrocalciferol, obtained by ultra-violet irradiation of pyrocalciferol and *iso*pyrocalciferol respectively (changes which are reversed on heating),[58] have been further examined by A. Windaus, K. Dimroth, and W. Breywisch.[59] The photoisomers contain two ethylenic linkages; during the photoisomerisation one of the nuclear ethylenic linkages of the pyrosterols is saturated with simultaneous formation of an unstable bridge. The irradiation of $\Delta^{6:8}$-cholestadienol has been further examined by G. Zuhlsdorff.[60]

Reduction of tachysterol (XXII) with sodium and propyl alcohol gives a mixture of dihydrovitamin-D_2 I (XXIII) and dihydro-

(XXII.)   (XXIV.)   (XXIII.)
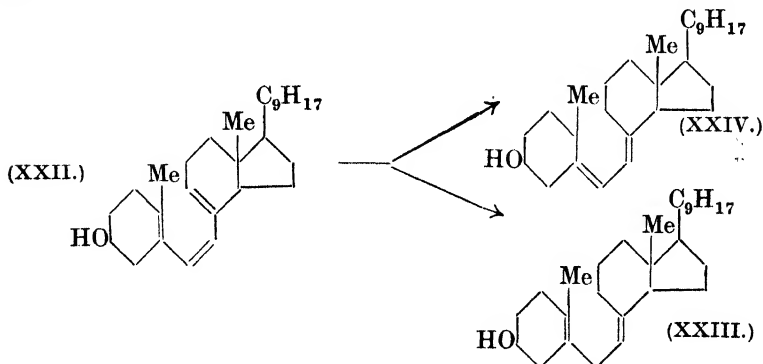
tachysterol (XXIV).[61] The latter is of interest in that it possesses in a high degree the property of raising the blood serum calcium

[57] *Annalen*, 1939, **542**, 204. [58] K. Dimroth, *Ber.*, 1937, **70**, 1631.
[59] *Annalen*, 1940, **543**, 240. [60] *Ber.*, 1940, **73**, 328.
[61] F. v. Werder, *Z. physiol. Chem.*, 1939, **260**, 119.

level; it is employed (A.T. 10) in the treatment of ideopathic and postoperative tetanies. The property of increasing the blood serum calcium level appears to be less specific than that of antirachitic activity, the former property appearing in tachysterol, tachysterol$_4$, dihydrotachysterol, vitamin-D$_2$, vitamin-D$_4$, and dihydrovitamin-D$_2$ II.

J. M. Bunker, R. S. Harris, and L. M. Mosher [62] conclude that 7-dehydrocholesterol is the significant provitamin-D of the skin. An isomer of 7-dehydrocholesterol, $\Delta^{4:6}$-cholestadienol, has been prepared by V. A. Petrow; [63] the product obtained from this dienol by irradiation with ultra-violet light does not show vitamin-D activity.

Other Sterols.—Brassicasterol, a diethenoid sterol isolated from rape-seed oil,[64] has been shown to be 3(β)-hydroxy-$\Delta^{5:22}$-ergostadiene (XXV) by E. Fernholz and H. E. Stavely.[65] Tetrahydrobrassicasterol is identical with ergostanol; ozonolysis of brassicasterol gives methyl*iso*propylacetaldehyde and oxidation of brassicasteryl acetate 5 : 6-dibromide gives 3(β)-hydroxybisnor-Δ^5-cholenic acid (XXVI).
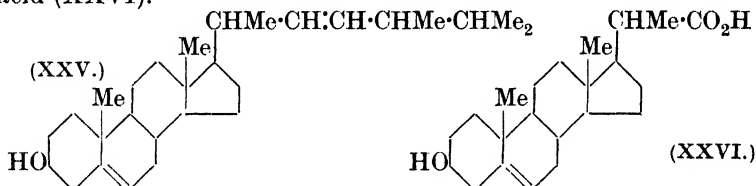
α-Spinasterol,[66] which has recently been isolated from alfalfa,[67] has been ascribed the structure (XXVII) by E. Fernholz and W. L. Ruigh.[68] Ozonolysis of α-spinasterol gives ethyl*iso*propylacetaldehyde, thus establishing the presence of a Δ^{22}-linkage. Dihydro-α-spinasterol (α-spinastenol) (XXVIII) is identical with the hydrogenation product of 7-dehydrostigmasterol (XXIX).[69]

The diethenoid sterol zymosterol isolated from yeast by I. Smedley-MacLean [70] has been examined by B. Heath-Brown, I. M. Heilbron, and E. R. H. Jones.[71] The sterol contains a readily

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[62] *J. Amer. Chem. Soc.*, 1940, **62**, 1760.

[63] *J.*, 1940, 66. [64] *Ber.*, 1909, **42**, 612.

[65] *J. Amer. Chem. Soc.*, 1939, **61**, 142; 1940, **62**, 428, 1875.

[66] M. C. Hart and F. W. Heyl, *J. Biol. Chem.*, 1932, **95**, 311; C. D. Larsen and F. W. Heyl, *J. Amer. Chem. Soc.*, 1934, **56**, 942; J. C. E. Simpson, *J.*, 1937, 730; C. D. Larsen, *J. Amer. Chem. Soc.*, 1938, **60**, 2431.

[67] E. Fernholz and M. L. Moore, *J. Amer. Chem. Soc.*, 1939, **61**, 2467; L. C. King and C. D. Ball, *ibid.*, p. 2910.

[68] *Ibid.*, 1940, **62**, 2341.

[69] O. Linsert, *Z. physiol. Chem.*, 1936, **241**, 125.

[70] *Biochem. J.*, 1920, **14**, 484; 1928, **22**, 22, 980. [71] *J.*, 1940, 1482.

reducible ethenoid linkage and an inert ethenoid linkage. The fully saturated zymostanol is identical with cholestanol and the reactive

$CHMe \cdot CH\colon CH \cdot CHEt \cdot CHMe_2$

Me

Me

HO

(XXVII.)

$CHMe \cdot [CH_2]_2 \cdot CHEt \cdot CHMe_2$

Me

Me

HO

(XXVIII.)

$CHMe \cdot CH\colon CH \cdot CHEt \cdot CHMe_2$

Me

Me

HO

(XXIX.)

$CHMe \cdot [CH_2]_2 \cdot CH\colon CMe_2$

Me

Me

HO

(XXX.)
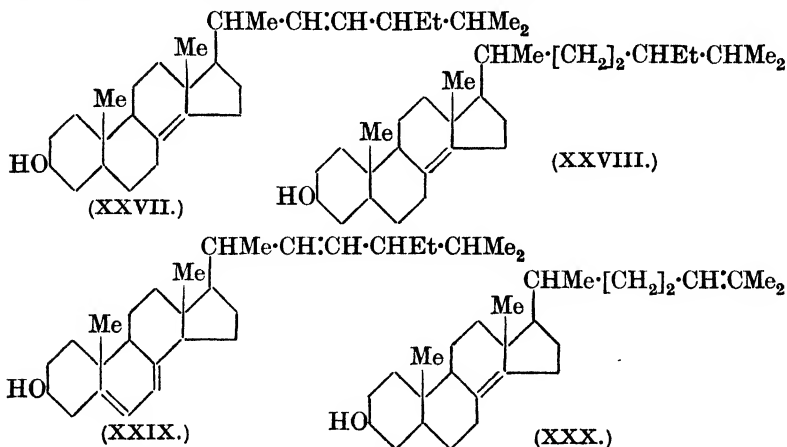
ethylenic linkage is situated in the side chain as an *iso*propylidene group, since ozonolysis of zymosterol gives acetone; similar treatment of dihydrozymosterol (α-zymostenol) does not give acetone. The last-mentioned derivative is almost certainly identical with α-cholestenol [72] obtained by partial reduction of 7-dehydrocholesterol; it is concluded that zymosterol is represented by the structure (XXX).

Treatment of the acetate-tetrabromides of both stigmasterol [73, 75] and brassicasterol [74] with sodium iodide gives the corresponding sterol 22 : 23-dibromides.

General.—The reduction of steroid ketones by the Wolff–Kischner method has been examined by J. D. Dutcher and O. Wintersteiner.[78] Whereas the semicarbazones of steroid 7- and 12-ketones behave normally, those of steroid 3-ketones give mainly the corresponding 3(α)-carbinols, this abnormal reaction being independent of the configuration at C_5. The abnormal reaction is completely suppressed by the addition of hydrazine hydrate; under these conditions cholestanone semicarbazone gives a quantitative yield of cholestane.

An interesting modification of the Oppenauer reaction [79] is

[72] F. Schenck, K. Buchholz, and O. Wiese, *Ber.*, 1936, **69**, 2696.

[73] E. Fernholz and H. E. Stavely, *J. Amer. Chem. Soc.*, 1939, **61**, 2956.

[74] *Idem, ibid.*, 1940, **62**, 428, 1875.

[75] E. Fernholz, W. L. Ruigh, and H. E. Stavely, *ibid.*, p. 1554.

[76] S. Bernstein and E. S. Wallis, *J. Org. Chem.*, 1937, **2**, 341; R. E. Marker and E. L. Wittle, *J. Amer. Chem. Soc.*, 1937, **59**, 2704.

[77] W. Discherl, *Z. physiol. Chem.*, 1939, **257**, 239.

[78] *J. Amer. Chem. Soc.*, 1939, **61**, 1992.

[79] R. V. Oppenauer, *Rec. Trav. chim.*, 1937, **56**, 137.

described by A. Wettstein.[80] Using benzoquinone instead of acetone or *cyclo*hexanone as hydrogen acceptor, he oxidised 3-hydroxy-Δ^5-steroid derivatives (XXXI) with aluminium *tert.*-butoxide to the corresponding $\Delta^{4:6}$-ketodienes (XXXII). It is shown that the Δ^4-3-ketones (XXXIII) which are the products of a normal Oppenauer oxidation of (XXXI) [79] cannot be intermediates in the new reaction, since they are unaffected when treated with aluminium *tert.*-butoxide with quinone as hydrogen acceptor. On the other hand, the Δ^5-3-

(XXXI.)   (XXXII.)
(XXXIII.)   (XXXIV.)
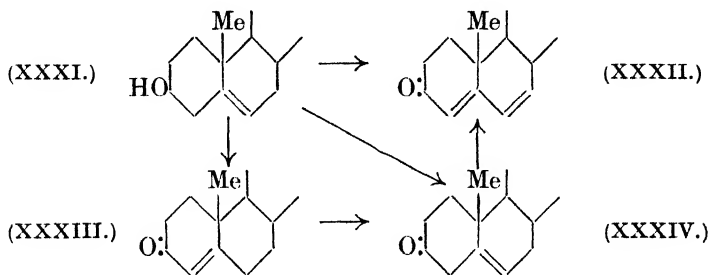
ketones (XXXIV) [81] are readily oxidised to the $\Delta^{4:6}$-3-ketones by the modified method.

By the action of sodium iodide on the *p*-toluenesulphonate or methanesulphonate of cholesterol, stigmasterol or sitosterol, B. Helferich and E. Günther [82] have obtained the corresponding steryl iodides. J. H. Beynon, I. M. Heilbron, and F. S. Spring [83] had previously obtained cholesteryl iodide by the action of hydriodic acid on *i*-cholesteryl methyl ether. 6-Iodocholesterol has been obtained by R. H. Levin and M. A. Spielman.[84]

It has been shown by R. P. Linstead [85] that, contrary to the suggestion of K. Miescher and W. H. Fischer,[86] there is no connection between the C_3-configuration of a sterol and its capacity to form a glucoside. W. Bergmann and F. Hirschmann [87] have formulated rules applicable in determining whether a steroid conjugated diene has its unsaturated system restricted to one ring or whether the system extends over two rings. $\Delta^{2:4}$-Cholestadiene has been shown to possess many of the chemical properties associated with the conjugated system of 7-dehydrocholesterol.[88]

F. S. S.

[80] *Helv. Chim. Acta*, 1940, **23**, 388.
[81] A. Butenandt, *Ber.*, 1936, **69**, 882, 889, 2773.
[82] *Ibid.*, 1939, **72**, 338, 932.   [83] *J.*, 1936, 907.
[84] *J. Amer. Chem. Soc.*, 1940, **62**, 920.   [85] *Ibid.*, p. 1766.
[86] *Helv. Chim. Acta*, 1938, **21**, 336.   [87] *J. Org. Chem.*, 1939, **4**, 40.
[88] W. Bergmann, F. Hirschmann, and E. L. Skau, *J. Org. Chem.*, 1939, **4**, 29; R. P. Jacobsen and C. Z. Nawrocki, *J. Amer. Chem. Soc.*, 1940, **62**, 2612.

8. HETEROCYCLIC COMPOUNDS.

General.

Structure.—V. Schomaker and L. Pauling [1] have determined the dimensions of several heterocyclic rings by electron-diffraction. The C–N distances in pyridine and pyrazine are greater than that calculated for 50% double-bond character, as if structures such as (I) and (II) were in resonance with the Kekulé forms, which would accord [2] with the chemical character of the nuclei and especially their resistance to ordinary substitution. In furan, thiophen, and pyrrole, the corresponding distances are in defect, relatively to the single-bond values, to an extent in accordance with contributions of very roughly 10, 34, and 24% from structures of the types (III) and (IV). The dipole moments, determined by H. de V. Robles,[3] indicate the values 15, 16, and 23% respectively. It is possible to attribute the discrepancy in the case of thiophen to the participation of structures such as (V, *a, b, c*) in which the sulphur octet has expanded to a decet.

$$\text{(I.)} \quad \text{(II.)} \quad \text{(III.)} \quad \text{(IV.)} \quad \text{(V.)} \; a \; b \; c$$
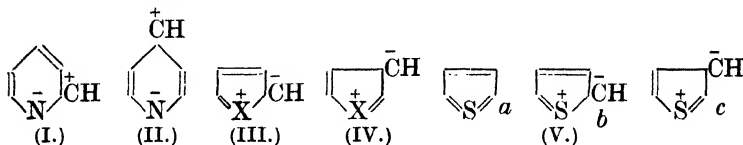
The resonance energy of the 5-rings has been re-assessed : furan, 23; thiophen, 31; pyrrole, 31 kg.-cals.

The peculiarity of rings containing sulphur has been explored from another direction.[4] Under standard conditions the following compounds exchanged for deuterium the hydrogen atoms of the italicised methyl groups only :

$$\text{(VI.)} \quad \text{(VII.)}$$
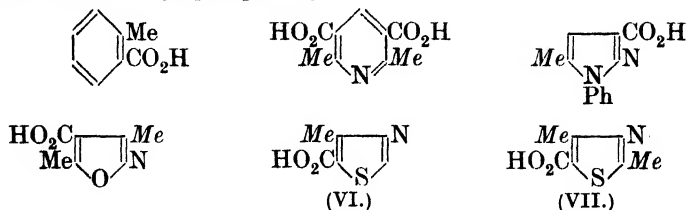
In general the hydrogen atoms of methyl side chains in nitrogen rings become mobile only when they are part of a system $\cdot N\ddot{:}C\cdot CH_3$ or its

[1] *J. Amer. Chem. Soc.*, 1939, **61**, 1769.

[2] C. Naegeli, W. Kündig, and H. Brandenburger, *Helv. Chim. Acta*, 1939, **22**, 912.

[3] *Rec. Trav. chim.*, 1939, **58**, 111; 1940, **59**, 184.

[4] H. Erlenmeyer and H. M. Weber, *Helv. Chim. Acta*, 1938, **21**, 863; H. Erlenmeyer, H. M. Weber, and P. Wiessmer, *ibid.*, p. 1017. See also H. Erlenmeyer and H. Ueberwasser, *ibid.*, 1940, **23**, 1268.

vinylogue; the reactivity of the 4-methyl radical in (VI) and (VII) becomes intelligible in terms of structures analogous to (V), but the data are too few as yet, and the inference is not the only possible one.

Basic Character.—The intense colour of cyanine dyes is attributed to resonance in the cation :
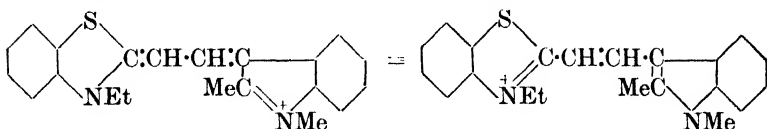
and the absorption of a dye having two different heterocyclic rings is commonly intermediate between those of the corresponding symmetrical pigments. In the case formulated, owing to the feeble basicity of the indole nucleus, the first form is subordinated, the resonance therefore limited, and the intensity of colour is less than that of either related symmetrical cyanine. In the bases of which the cyanines are quaternary salts, the structure involving a bicovalent anionic nitrogen atom will be in general disfavoured, and the bases are lighter in colour [5] than their alkyliodides or their salts with acids :

(I.)
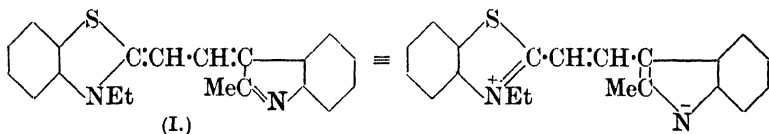
In this particular case, however, the character of the indole nucleus that hindered the resonance of the salt favours that of the base, which is now the more highly coloured of the two. On the other hand the base (II), from dealkylation of the thiazole ring, is colourless. The series (III), (IIIa), (IV) shows a similar relationship.

(II.)

(III.) Bluish-purple.

(IIIa.) Rather paler.

(IV.) Pale yellow.
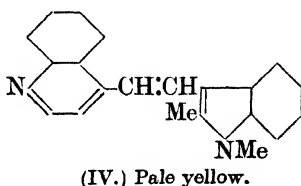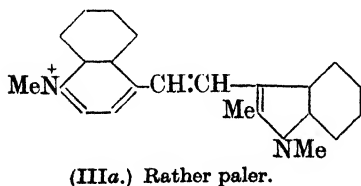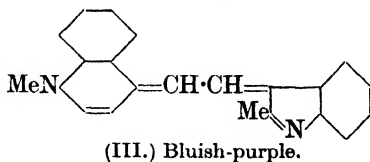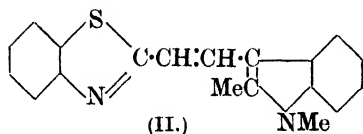
[5] L. G. S. Brooker, R. H. Sprague, C. P. Smyth, and G. L. Lewis, *J. Amer. Chem. Soc.*, 1940, **62**, 1116.

This interpretation is reinforced by the measured dipole moments of the bases : contrast (I) (7·68 D.) with (II) (4·06) and (III) (10·6) with (IV) (5·43); the values for the non-ionic structures would be 2—2·5 D., and for the betaines 20—30 D.

(Miss) F. M. Hamer [6] has thoroughly investigated the methods available for the preparation of symmetrical and unsymmetrical bases of this kind, and finds that substances of the type (V) are yellow and deepen in colour in presence of acids, whereas those of the type (VI) are orange and unaffected by acidification. The distinction is in the direction to be expected, but is surprisingly emphatic.
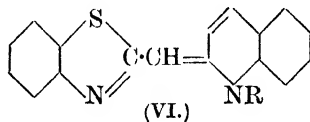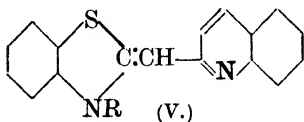
When di-β-naphtha*spiro*pyran (VII) is heated in inert solvents, an intense colour develops, attributed to an intramolecular ionisation which is reversed on cooling : [7]
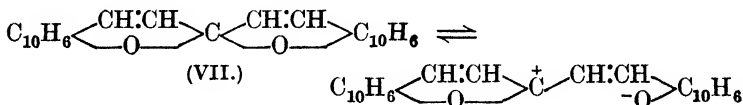
The process may be regarded as a function of the basic character of the central carbon atom or of the left-hand ring as a whole. Of the following naphthapyrans,[8] the first two show no sign of ionisation, the last three are coloured even in the solid state, and the others develop colour in solution at progressively lower temperatures :
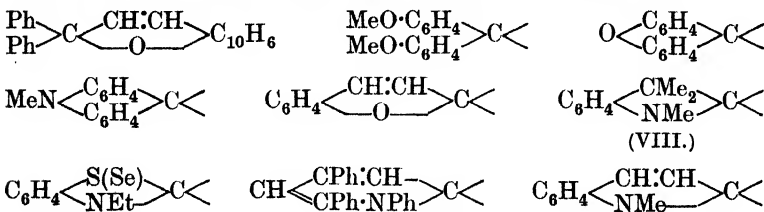
Valency Angles and Ring Closure.—Lüttringhaus [9] uses facility of ring closure in order to assess the distance between the oxygen atoms

[6] *J.*, 1940, 799.

[7] See, *e.g.*, R. Dickinson and I. M. Heilbron, *J.*, 1927, 1699.

[8] R. Wizinger and H. Wenning, *Helv. Chim. Acta*, 1940, **23**, 247.

[9] A. Lüttringhaus, *Annalen*, 1937, **528**, 211, 223; *Ber.*, 1939, **72**, 887; R. Kohlhaas and A. Lüttringhaus, *ibid.*, pp. 897, 907; A. Lüttringhaus and K. Buchholz, *Ber.*, 1939, **72**, 2057; 1940, **73**, 134.

and therefore the C–X–C valency angles in compounds of the type p-HO·C$_6$H$_4$·X·C$_6$H$_4$·OH. Under standard conditions the substances HO·C$_6$H$_4$·X·C$_6$H$_4$·O·[CH$_2$]$_n$Br give the following percentage yields of monomeric ether O·C$_6$H$_4$·X·C$_6$H$_4$·O·[CH$_2$]$_n$:

X.	5	6	7	8	10	12	X.	5	6	7	8	10	12
O	—	0	—	0	36	—	CH$_2$	—	—	5	27	68	—
S	—	0	—	16	51	—	CMe$_2$	—	0	—	24	54	—
SO$_2$	6	10	—	—	24	—	CO	—	0	—	—	0	11·5

The indication of a small valency angle for S in the sulphone is notable, and also the absence of any evidence for the Thorpe–Ingold effect in the case of CMe$_2$. An X-ray study of the cyclic ether, X = S; n = 10, gave the C–S–C angle 112·4° $\pm$ 1·5° and this value has been combined with the chemical data to estimate the angle in other cases. Thus for X = CH$_2$; n = 8, the yield is 27% ; by interpolation, the same yield corresponds to the imaginary case X = S; n = 8·6. Given the C–S–C angle of 112·4°, the distance c (I) will be 9 A., and the corresponding distance for the methylene compound is taken to be 9 A. $\times$ 8/8·6 ; whence the C–CH$_2$–C angle is 110° $\pm$ 3°, as it should be. A similar calculation gives 133° for C–O–C, corrected on somewhat subjective grounds to 129° $\pm$ 4°.
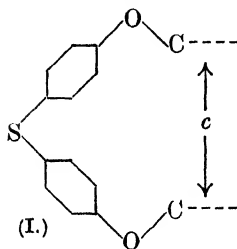
The possibility of isomorphous replacement of O, S, and CH$_2$ in their diaryl derivatives and in the cyclic structures just mentioned appears to depend on similarity of valency angle; [10] but when similar angles are constrained, as in fluorene and diphenylene oxide and sulphide, complete miscibility is observed. N. M. Cullinane and W. T. Rees [11] come to similar conclusions in a study of systems

$$C_6H_4 \!\!<_Y^X\!\!> C_6H_4 \quad (X, Y = O, S, NH).$$

isoIndoles and isoBenzfurans.—Their relation to phthalocyanines (see p. 316) has stimulated work on *iso*indoles and led incidentally to the demonstration [12] that the only simple unreduced *iso*indole on record is really a dihydro-derivative, further emphasising the contrast with the readily formed indole system. Phthalonitrile is the starting point for *iso*indole syntheses of a new type; with methyl-lithium or methylmagnesium iodide [13] the strongly basic

[10] A. Lüttringhaus and K. Hauschild, *Ber.*, 1940, **73**, 145.

[11] *Trans. Faraday Soc.*, 1940, **36**, 507 ; N. M. Cullinane and C. A. J. Plummer, *J.*, 1938, 63.

[12] R. P. Linstead and E. G. Noble, *J.*, 1937, 933.

[13] P. A. Barrett, R. P. Linstead, and G. A. P. Tuey, *J.*, 1939, 1809; *idem* and F. G. Rundall, *J.*, 1940, 1079.

1-amino-3 : 3-dimethyl-ψ-*iso*indole is formed, probably by the following stages :

$$C_6H_4\!\!\begin{array}{c}\diagup CN\\ \diagdown CN\end{array} \longrightarrow C_6H_4\!\!\begin{array}{c}\diagup CMe\!:\!NLi\\ \diagdown CN\end{array} \longrightarrow C_6H_4\!\!\begin{array}{c}\diagup CMe\\ \diagdown C\!:\!NLi\end{array}\!\!>\!\!N \longrightarrow$$

$$C_6H_4\!\!\begin{array}{c}\diagup CMe_2\\ \diagdown C\!:\!NLi\end{array}\!\!>\!\!NLi \longrightarrow C_6H_4\!\!\begin{array}{c}\diagup CMe_2\\ \diagdown C\!\cdot\!NH_2\end{array}\!\!>\!\!N$$

Acetylation, followed by hydrolysis, yielded dimethyl*iso*indolinone. Phthalonitrile reacts in an analogous fashion with the sodio-derivatives of phenylacetonitrile or ethyl cyanoacetate or malonate, the first stage being a Thorpe reaction : [14]

$$C_6H_4\!\!\begin{array}{c}\diagup CN\\ \diagdown CN\end{array} \longrightarrow \left[C_6H_4\!\!\begin{array}{c}\diagup C\!\cdot\!CH(CO_2Et)_2\\ \diagdown CN\end{array}\!\!>\!\!NH \right] \longrightarrow C_6H_4\!\!\begin{array}{c}\diagup C\!:\!C(CO_2Et)_2\\ \diagdown C\!:\!NH\end{array}\!\!>\!\!NH$$

dil. acid ↙   ↓ KMnO₄

Phthalimide

$$C_6H_4\!\!\begin{array}{c}\diagup C\!:\!CH\!\cdot\!CO_2H\\ \diagdown CO\end{array}\!\!>\!\!NH \xleftarrow[\text{alkali}]{} C_6H_4\!\!\begin{array}{c}\diagup C\!:\!C(CO_2Et)_2\\ \diagdown CO\end{array}\!\!>\!\!NH \quad (II.)$$

The ester (II) can also be prepared from iminophthalimidine,

$$C_6H_4\!\!\begin{array}{c}\diagup C\!:\!NH\\ \diagdown CO\end{array}\!\!>\!\!NH,$$ and ethyl malonate ; [15] ethyl acetoacetate behaves

similarly. With hydrogen sulphide, phthalonitrile affords [16] the

$$C_6H_4\!\!\begin{array}{c}\diagup C\!=\!\!=\!\!=\!\!C\\ \diagdown C\!\cdot\!SH\end{array}\!\!\begin{array}{c}>\!\!N \quad N\!\!<\\ HS\!\cdot\!C\end{array}\!\!>\!\!C_6H_4$$
(III.)

binuclear *iso*indole derivative (III), which condenses readily with reactive methylene compounds with elimination of hydrogen sulphide.

Apparently contradictory results in the investigation of methylene- and carboxymethylene-*iso*indolinones (-phthalimidines) were explained by the unravelling [15] of the following series of preparatively useful transformations :

$$C_6H_4\!\!\begin{array}{c}\diagup C\!:\!CH\!\cdot\!CO_2H\\ \diagdown CO\end{array}\!\!>\!\!O \xrightarrow[\text{NH}_3]{} C_6H_4\!\!\begin{array}{c}\diagup CO\!\cdot\!CH_2\!\cdot\!CO_2NH_4\\ \diagdown CO\!\cdot\!NH_2\end{array}$$

acid (room temp.) ↓   │ ↓ *acid (0°)*

$$C_6H_4\!\!\begin{array}{c}\diagup CO\!\cdot\!CH_2\!\cdot\!CO_2H\\ \diagdown CO\!\cdot\!NH_2\end{array} \xrightarrow[\text{hot water}]{} C_6H_4\!\!\begin{array}{c}\diagup C\!:\!CH_2\\ \diagdown CO\end{array}\!\!>\!\!NH$$

$$\text{Phthalimide} \xleftarrow[\text{KMnO}_4]{} C_6H_4\!\!\begin{array}{c}\diagup C\!:\!CH\!\cdot\!CO_2H\\ \diagdown CO\end{array}\!\!>\!\!NH \xrightarrow[\text{Na-Hg}]{} C_6H_4\!\!\begin{array}{c}\diagup CH\!\cdot\!CH_2\!\cdot\!CO_2H\\ \diagdown CO\end{array}\!\!>\!\!NH$$

[14] P. A. Barrett, R. P. Linstead, J. J. Leavitt, and G. A. Rowe, *J.*, 1940, 1076.
[15] R. P. Linstead and G. A. Rowe, *J.*, 1940, 1070.
[16] Imperial Chem. Ind., *B*, 1940, 192, 349, 434.

In contrast to *iso*indoles, 3 : 4-benzfurans (*iso*benzfurans) are known, at least when arylated in the furan ring; they are yellow and fairly stable, but polymerise easily, and it is suggested on the basis of optical data that free radicals (V) may be concerned.[17] The relatively ready formation of this system is illustrated by the production of *iso*benzfurans from phenolphthalins (triphenyl-methane-*o*-carboxylic acids) and sulphuric acid, a reaction involving migration of an aryl radical.[18] A new method for their synthesis is based on the Diels–Alder reaction : [19]

Butadiene +
trans-CHBz:CHBz

$$CH_2$$
$$CH \quad CH\cdot COPh$$
$$CH \quad CH\cdot COPh$$
$$CH_2$$

Ac$_2$O–H$_3$PO$_4$

(V.)

Br$_2$–
NaOAc

Zn–NaOH

(IV.)

maleic
anh.

(two stereoisomerides)

HOAc

1 : 4-Diphenylnaphthalene
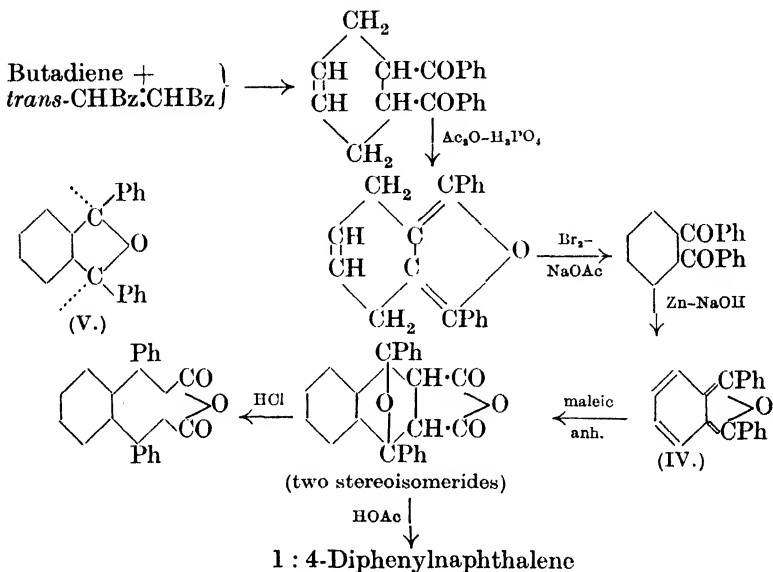
The *iso*benzfurans (IV) themselves undergo the diene-synthesis with ethyl cinnamate, acraldehyde, and especially maleic anhydride, giving derivatives of 1 : 4-diphenylnaphthalene [19, 20] not readily obtained otherwise. The analogous addition of α-naphthaquinone to (IV) affords diphenylnaphthacenequinone.[21] With phosphorus pentasulphide, (IV) yields the related *iso*benzthiophen,[22] which does not add maleic anhydride, and is identical with the supposed " mesothioanthracen-dihydrid " of A. Bistrzycki and B. Brenken.[23]

[17] R. Adams and M. H. Gold, *J. Amer. Chem. Soc.*, 1940, **62**, 2038.

[18] F. F. Blicke and R. A. Patelski, *J. Amer. Chem. Soc.*, 1936, **58**, 276, 559.

[19] R. Adams and T. A. Geissman, *ibid.*, 1939, **61**, 2083 ; R. Adams and M. H. Gold, *ibid.*, 1940, **62**, 56 ; R. Adams and R. B. Wearn, *ibid.*, p. 1233.

[20] R. Weiss and A. Beller, *Monatsh.*, 1932, **61**, 143 ; R. Weiss and A. Abeles, *ibid.*, p. 162 ; C. Dufraisse and R. Priou, *Bull. Soc. chim.*, 1938, **5**, 502.

[21] C. Dufraisse and P. Compagnon, *Compt. rend.*, 1938, **207**, 585.

[22] C. Dufraisse and D. Daniel, *Bull. Soc. chim.*, 1937, **4**, 2063.

[23] *Helv. Chim. Acta*, 1922, **5**, 20.

W. Dilthey, E. Graef, H. Dierichs, and W. Josten [24] describe the corresponding phenanthrathiophen.

Natural Products Containing Oxygen Rings.

Coumaranones and Flavones.—*Didymocarpus pedicellata* affords derivatives of pentahydroxybenzene.[25] The constitution of pedicellin (I; R = Me) is well established; pedicin, of which pedicellin is the dimethyl ether, is probably (I; R = H); and *iso*pedicin and ψ-*iso*pedicin are possibly the active and the racemic form of the related coumaranone (II).

(I.)   MeO⟨RO OR⟩CO·CH:CHPh   MeO⟨HO O⟩CO·CH·CH₂Ph (II.)
    MeO OMe   MeO OMe
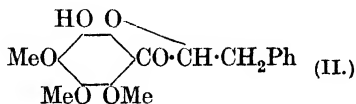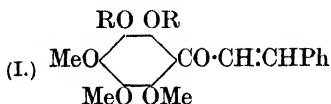
The carmine-red constituent pedicinin, also obtained by oxidation and hydrolysis of pedicellin, was formulated as the benzylidene-coumaranone (III), but P. K. Bose and P. Dutt [26] give cogent arguments in favour of the structure (IV).

(III.) MeO⟨HO O⟩CO·C:CHPh   (IV.) HO/MeO⟨⟩CO·CH:CHPh
    HO OH   O
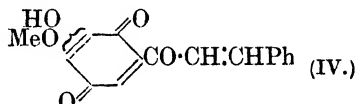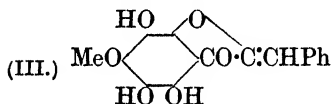
The view that primetin is 5 : 8-dihydroxyflavone has now been confirmed by synthesis [27] of the 8-monomethyl ether (VI). Oxidation of 2 : 6-dihydroxyacetophenone or its monobenzyl ether with persulphate, followed by methylation and partial hydrolysis, afforded 2-hydroxy-3 : 6-dimethoxyacetophenone (V) :

(V.) ⟨OMe OH CO·CH₃ OMe⟩ → ⟨OMe O CPh CH OMe CO⟩ ⇌(AlCl₃/Me₂SO₄) ⟨OMe O CPh CH OH CO⟩ (VI.)
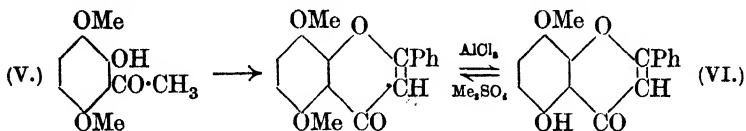
Friedel–Crafts acetylation of 1 : 2 : 3 : 5-tetramethoxybenzene is accompanied by demethylation, and the resulting 2-hydroxy-3 : 4 : 6-trimethoxyacetophenone affords, *via* its anisylidene derivative, 5 : 7 : 8 : 4'-tetramethoxyflavanone (carthamidin tetramethyl ether).[28] Synthetic 5 : 8 : 4'-trimethoxyflavone is not identical with

[24] *J. pr. Chem.*, 1939, **151**, 185.
[25] S. Siddiqui, *J. Indian Chem. Soc.*, 1937, **14**, 703; V. Sharma and S. Siddiqui, *ibid.*, 1939, **16**, 1; S. Warsi and S. Siddiqui, *ibid.*, p. 519.
[26] *Ibid.*, 1940, **17**, 499.
[27] W. Baker, N. C. Brown, and J. A. Scott, *J.*, 1939, 1922; Z. Horii, *J. Pharm. Soc. Japan*, 1939, **59**, 209.
[28] G. Bargellini, *Atti X Congr. Internaz. Chim.*, 1938, III, 32.

the dimethyl ether of ginkgetin, from the leaves of the Maidenhair tree; exclusion of other alternatives and reconsideration of the analytical data suggest that ginkgetin may contain three extra carbon atoms and an additional ring.[29]

The glucose residue of gossypitrin is in position 7,[30] since the glucoside on methylation and hydrolysis affords 7-hydroxy-$3:5:8:3':4'$-pentamethoxyflavone agreeing in properties with synthetic material.[31] Lespedin, isolated from *Lespeza cryptobotrya*, and doubtfully identical with campheritrin, is a dirhamnoside of camphcrol. With diazomethane it yields a monomethyl ether readily and a dimethyl ether with difficulty; hydrolysis of the former affords campherol 4'-monomethyl ether, and it is inferred that the rhamnose residues are in the 3- and 7-positions.[32]

Pterocarpin and homopterocarpin, colourless constituents of red sandalwood, are chromanocoumarans,[33] the latter, more abundant, substance being (VII; $R_1 = OMe$, $R_2 = H$).

(VII.)   (VIII.)

(IX.)   (X.)
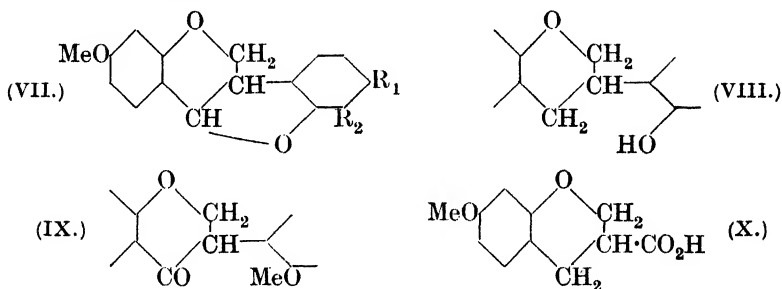
The four oxygen atoms of homopterocarpin are indifferent, but reduction yields a phenolic dihydrohomopterocarpin (VIII) which can be oxidised to a *p*-quinone and also to the acid (X).   Oxidation of the methyl ether of (VIII) affords the *iso*flavanone (IX), which has been synthesised as follows [$R = 2:4$-$(MeO)_2C_6H_3$] :

$$R \cdot CH_2 \cdot CN + \text{resorcinol} \} \longrightarrow \quad \xrightarrow[\substack{\text{Na-} \\ \text{H·CO}_2\text{Et} \\ \text{on Me}_i \\ \text{ether}}]{}$$
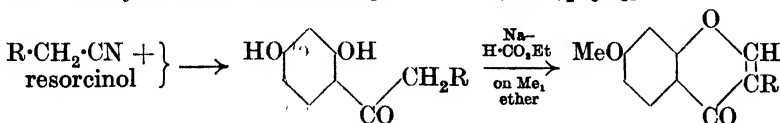
The *iso*flavone is reduced catalytically to the methyl ether of (VIII) and then oxidised to (IX).   Pterocarpin contains a methylene-

[29] W. Baker and W. H. C. Simmonds, *J.*, 1940, 1370.

[30] P. S. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 1939, *A*, **9**, 177.

[31] W. Baker, R. Nodzu, and (Sir) R. Robinson, *J.*, 1929, 74.

[32] S. Hattori and M. Hasegawa, *Proc. Imp. Acad. Tokyo*, 1940, **16**, 9.

[33] E. Späth and J. Schläger, *Ber.*, 1940, **73**, 1; A. McGookin, A. Robertson, and W. B. Whalley, *J.*, 1940, 787.

dioxy-group and shows similar reactions to those of its associate;
it is formulated as (VII; $R_1R_2 = CH_2O_2$), the orientation following
from the production of a p-quinone from dihydropterocarpin.

Furano- and Pyrano-compounds.—Nodakenin, from *Peucedanum
decursivum*, is the glucoside of nodakenetin, from which it has been
resynthesised. Nodakenetin by dehydration and reduction affords
the known lactone (I), the relative stability to dehydration showing
that the hydroxyl group is not in the furan ring; and the production
of acetone on oxidation defines the structure as (II).[34]
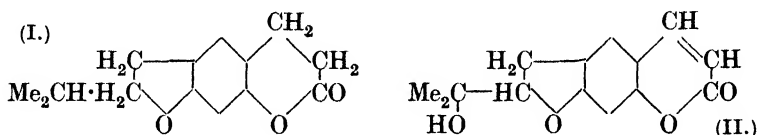
It has now been shown that the linearly constituted xanthyletin
(III) accompanies its angular isomeride seselin in the synthesis of
the latter from methylbutinol and umbelliferone : [35]
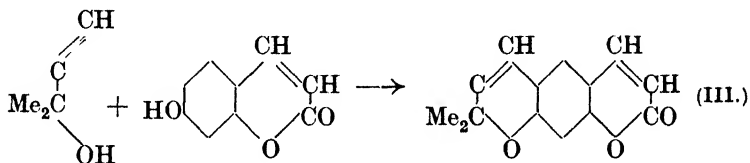
The formation of methyl *iso*propyl ketone by oxidation of dun-
nione establishes the structure (IV) for the latter.[36] Migration of
a methyl group from the β- to the α-position in the furan ring
probably takes place in the conversion into β-*iso*dunnione, which
yields acetone on oxidation.
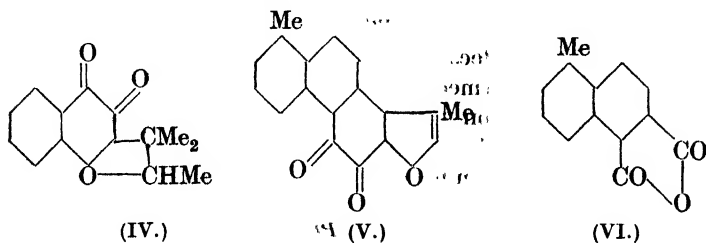
[34] E. Späth and P. Kainrath, *Ber.*, 1936, **69**, 2062; E. Späth and (Frl.
E. Tyray, *Ber.*, 1939, **72**, 2089.

[35] E. Späth and R. Hillel, *Ber.*, 1939, **72**, 963, 2093; compare *Ann. Reports*,
1939, **36**, 316.

[36] J. R. Price and (Sir) R. Robinson, *J.*, 1940, 1493.

A phenanthrafuran system seems to be present in tanshinone I, a constituent of the Chinese drug *tan-shin*. The substance is an *o*-quinone, not easily hydrogenated beyond the stage of quinol, and yields on oxidation the anhydride (VI). The third oxygen atom is indifferent, two *C*-methyl groups are present, and tanshinone I is almost certainly (V) or a position isomeride.[37]

Usnic Acid.[38]—The nature of the side chain in decarbousnic acid (I; R = Me) is confirmed by the demonstration that the related acetousnetic ester (I; R = OEt) is a γ- and not an α-substituted acetoacetic ester.[39]

(I.)   (II.)
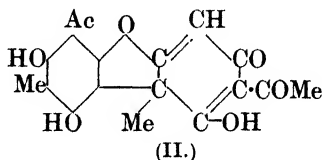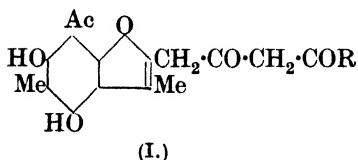
Usnic " acid " (which is not a carboxylic acid) yields decarbousnic acid by simple heating with alcohol at 150°—$C_{18}H_{16}O_7 + H_2O \longrightarrow C_{17}H_{18}O_6 + CO_2$; since its optical activity persists in alkaline solution, the additional carbon atom is probably linked in such a way as to give rise to an asymmetric centre in the coumarone nucleus, with disturbance of the aromatic conjugation of one or both rings. F. H. Curd and A. Robertson,[40] and R. T. Foster, A. Robertson, and T. V. Healy [41] propose the formula (II), which accounts for the production of an α-coumaranone and oxaloacetic acid on ozonisation.[42] Many reactions of usnic acid then imply facile opening of the dihydrobenzene ring, attributed to mobility caused by the quaternary carbon atom and the tendency to form a normal coumarone system. Sulphuric acid converts usnic and decarbousnic acids respectively into usnolic acid (a true carboxylic acid) and decarbousnol. On the basis of the formula (II) the dihydrobenzene ring opens and re-closes to (III; R = CO₂H), decarbousnol being (III; R = H).

This has been confirmed by model experiments in which (IV; R = H or Me) gave on treatment with sulphuric acid products closely resembling usnolic acid, in the formation of which, therefore, neither the 7-carbon atom nor the attached acetyl group is involved.

[37] M. Nakao and T. Fukushima, *J. Pharm. Soc. Japan*, 1934, **54**, 844; F. von Wessely and S. Wang, *Ber.*, 1940, **73**, 19.
[38] *Ann. Reports*, 1938, **35**, 314.
[39] Y. Asahina and M. Yanagita, *Ber.*, 1939, **72**, 1140.
[40] *J.*, 1937, 894.
[41] *J.*, 1939, 1594.
[42] C. Schöpff and F. Ross, *Naturwiss.*, 1938, **26**, 772.

Y. Asahina [43] has discussed the transformations of usnic acid and proposes among others the structure (V).
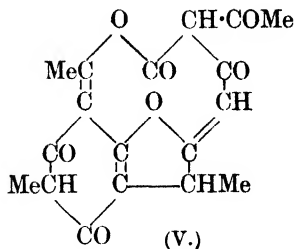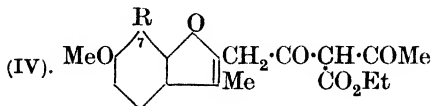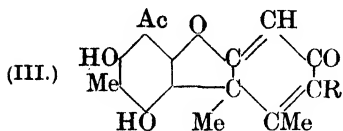
Cannabinol.—Earlier work [44] established the structure (I), apart from the orientation of the substituents in the right-hand nucleus. It is now found [45] that both in hashish and in American wild hemp (marihuana) cannabinol is accompanied by the dihydric phenol cannabidiol, the structure of which has been largely elucidated.[46, 47] The phenol can be decomposed into *p*-cymene and olivetol (5-*n*-amylresorcinol), and it is hydrogenated to tetrahydrocannabidiol, which yields menthane-3-carboxylic acid on oxidation. The absorption spectrum indicates that no double bond is conjugated with the aromatic nucleus; and, by comparison with those of synthetic materials, that cannabidiol is a 2-substituted resorcinol. Cannabidiol, which yields formaldehyde in quantity on ozonolysis and does not combine with maleic anhydride, is provisionally formulated as (II).
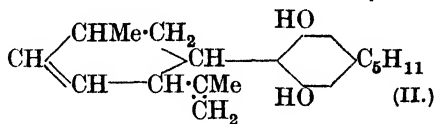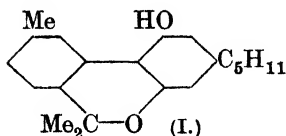
Acids convert cannabidiol into a variable mixture of isomeric tetrahydrocannabinols, dehydrogenated to cannabinol itself.[47, 48] The orientation (I) for cannabinol, already rendered probable by

[43] *Proc. Imp. Acad. Tokyo*, 1939, **15**, 311.

[44] *Ann. Reports*, 1932, **29**, 191.

[45] (Miss) A. Jacob and A. R. Todd, *J.*, 1940, 649; R. Adams, D. C. Pease, and J. H. Clark, *J. Amer. Chem. Soc.*, 1940, **62**, 2194.

[46] R. Adams, C. K. Cain, J. H. Clark, M. Hunt, and H. Wolff, *ibid.*, pp. 196, 732, 735, 1770, 2215.

[47] R. Adams *et al.*, *ibid.*, p. 2566.

[48] R. Adams, D. C. Pease, C. K. Cain, and J. H. Clark, *J. Amer. Chem. Soc.*, 1940, **62**, 2402; *idem*, B. R. Baker, H. Wolff, and R. B. Wearn, *ibid.*, p. 2245.

its absorption spectrum and colour reactions, is thus confirmed. Following much exploratory work, cannabinol was synthesised independently by both groups of investigators :

A [49]

B [50]
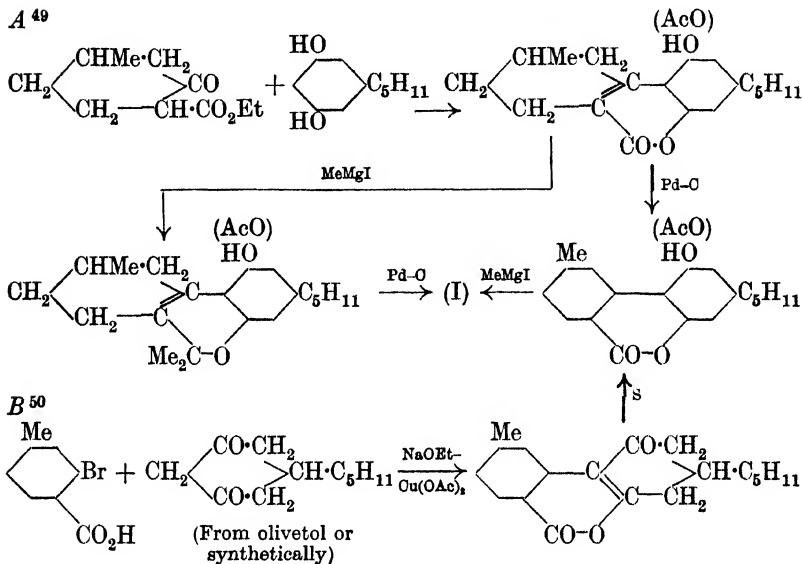
Alkaloids.

Pyrrolidine and Piperidine Bases.—The minor bases of *Lobelia inflata* have been further studied.[51] *dl*-Lelobanidine has been degraded to the diketone $Bz \cdot [CH_2]_7 \cdot COEt$, independently synthesised, and to 1-methylpiperidine-2-carboxylic-6-acetic acid, whence it is formulated as (I). The other alkaloids are related to it in much the same way as the previously studied C_{21} and C_{22} bases to lobelanidine (I, with Ph for Et).
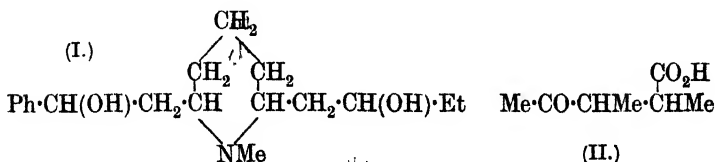
[49] R. Ghosh, A. R. Todd, and S. Wilkinson, *J.*, 1940, 1121, 1393; compare also R. Adams, and B. R. Baker, *J. Amer. Chem. Soc.*, 1940, **62**, 2401; G. Powell and T. H. Bembry, *ibid.*, p. 2568.

[50] R. Adams, B. R. Baker, and R. B. Wearn, *ibid.*, p. 2204.

[51] O. Thomä, *Annalen*, 1939, **540**, 99; H. Wieland, W. Kosehara, (Frl.) E. Dane, J. Renz, W. Schwarze, and W. Linde, *ibid.*, p. 103.

Senecio species have furnished a number of new alkaloids, several of which are esters of retronecine.[52] Monocrotaline, the alkaloid of *Crotalaria spectabilis* and *C. retusa*, affords retronecine, monocrotic acid, and carbon dioxide on hydrolysis, and retronecanol and monocrotalic acid on reduction. The former acid (II) has been synthesised, and it is concluded that the latter is (III).[53] Heliotric acid from heliotrine has been shown to be (IV).[54]

$$\text{(III.)} \quad \underset{\underset{\text{O}\rule{3cm}{0.4pt}}{}}{\overset{\overset{\text{OH} \qquad \text{CO}_2\text{H}}{}}{\text{Me·C·CHMe·CMe·CO}}} \qquad\qquad \underset{\overset{}{\text{CO}_2\text{H}}}{\overset{\overset{\text{OH} \quad \text{OMe}}{}}{\text{CHMe}_2\text{·C}\rule{1cm}{0.4pt}\text{CHMe}}} \quad \text{(IV.)}$$
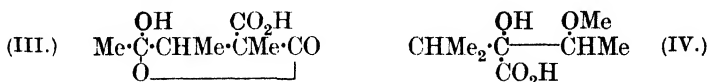
N-Methylpyrrolidine has been isolated from tobacco, and it has been shown that *iso*nicoteine is 2 : 3′-dipyridyl.[55] A new synthesis of *r*-lupinine (VI) is recorded; picolinoyl chloride, by the successive action of diazomethane and acid, yields picolinoylcarbinol, which with γ-ethoxypropylmagnesium bromide affords (V).[56]

$$\text{(V.)} \qquad \xrightarrow[\text{then III}]{\text{H}_2\text{–PtO}_2} \qquad \text{(VI.)}$$
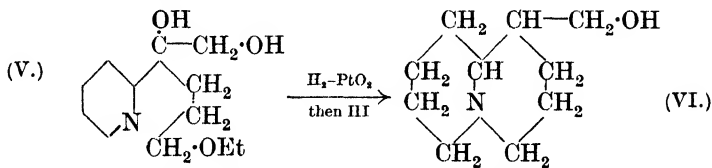
Benzylisoquinoline Alkaloids.—Cheilanthifoline,[57] obtained from *Corydalis* species, is (I), since its methyl ether is identical with sinactine, and its ethyl ether can be oxidised to the known lactam (II).
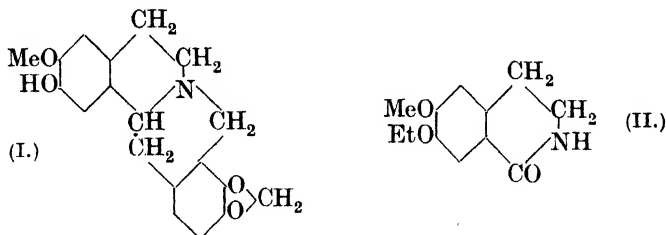
Cryptocavine yields, by Emde reduction of the methosulphate, followed by dehydration and oxidation of the resulting carbinol, the same products as are obtained by similar treatment of the isomeric

[52] R. H. F. Manske, *Canadian J. Res.*, 1939, **17**, *B*, 1, 8; H. L. de Waal, *Nature*, 1940, **146**, 777.

[53] R. Adams, R. S. Long, C. F. Rogers, and F. J. Sprules. *J. Amer. Chem. Soc.*, 1939, **61**, 2815, 2819, 2822; 1940, **62**, 2289.

[54] G. P. Menschikov, *J. Gen. Chem. Russia*, 1939, **9**, 1851.

[55] E. Späth and S. Biniecki, *Ber.*, 1939, **72**, 1809.

[56] K. Winterfeld and H. von Cosel, *Arch. Pharm.*, 1940, **278**, 70.

[57] R. H. F. Manske, *Canadian J. Res.*, 1940, **18**, *B*, 100.

cryptopine; and it is regarded as (III), in which the carbonyl and the adjacent methylene group of cryptopine are interchanged.[58]

(III.)   (IV.)
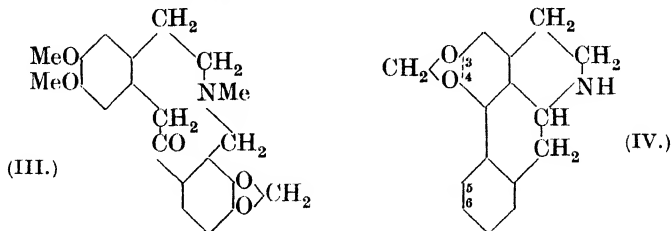
Anonaine, from *Anona reticulata*, is (IV).[59] The inactive base has been synthesised by standard methods, and, although it could not be resolved, it yielded on Hofmann degradation the same nitrogen-free product as the natural alkaloid. *Rœmeria refracta* affords the base rœmerine, which appears to be *N*-methylanonaine; there is fair agreement as to the properties of common transformation products. The demethylenated base is not identical with apo-morphine (the 5 : 6-dihydroxy-analogue); its degradation by exhaustive methylation proceeds as usual in this series and affords ultimately the known 3 : 4-dimethoxyphenanthrene, thus locating the methylenedioxy-group of the original alkaloid.[60]

The relative positions of the hydroxyl and methoxyl groups in bebeerine (V) have now been established by Hofmann degradation and oxidation of bebeerine diethyl ether, which afforded the acids (VI) and (VII), identified by synthesis.[61]

The alkaloids of several *Chondrodendron* species have been thoroughly examined, primarily in order to establish the botanical provenance of the drug *radix pareiræ bravæ*.[62] Protocuridine and *iso*chondrodendrine give the same product on methylation and are isomeric dimethyl ethers of (VIII), as is also *neo*protocuridine, which affords the same *O*-methylmethine as *iso*chondrodendrine. The first two active bases belong to the same stereochemical series; and the last is internally compensated. The new alkaloid chondrofoline is a trimethyl ether related to (V), since it gives an *O*-methylmethine methiodide, also obtained from bebeerine. A group of bisbenzyl-*iso*quinoline alkaloids may be classified as follows :

	Bebeerine type (V).	*iso*Chondrodendrine type (VIII)
Asymmetric centres of same sign	*d*-Bebeerine	*d-iso*Chondrodendrine
	l-Bebeerine (*l*-curine)	*O*-Methyl*iso*chondrodendrine
	l-Chondrofoline	*d*-Protocuridine
Opposite sign	*i-neo*Protocuridine	*d*-Tubocurarine

[58] R. H. F. Manske and L. Marion, *J. Amer. Chem. Soc.*, 1940, **62**, 2042.

[59] G. Barger and G. Weitnauer, *Helv. Chim. Acta*, 1939, **22**, 1036.

[60] S. Junusov, R. A. Konovalova, and A. P. Orékhov, *J. Gen. Chem. Russia*, 1939, **9**, 1356, 1507, 1868.

[61] H. King, *J.*, 1939, 1157.   [62] H. King, *J.*, 1940, 737.

Radix pareiræ bravæ also contains the simpler base *d-iso*coclaurine, which is (IX), since it yields the same dimethyl ether methiodide as the known coclaurine, and gives no catechol reaction.

(V.)

(VI.)

(VII.)

(VIII.)

(IX.)
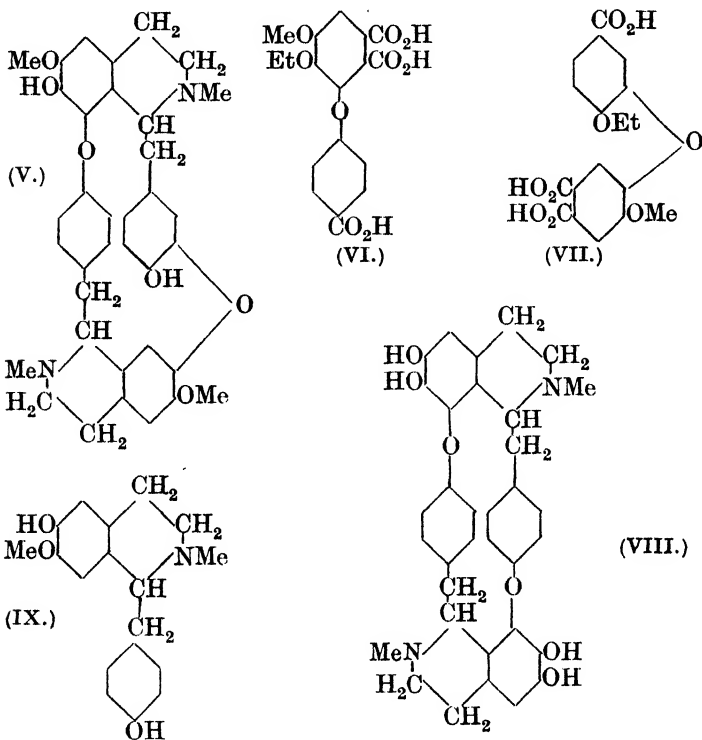
Tetrandrine, in which the benzyl*iso*quinoline systems are joined head to head and tail to tail, is the methyl ether of the new alkaloid fangchinoline; both occur in the Chinese drug *Han-fang-chi*. Oxidation of tetrandrine or of fangchinoline ethyl ether yields 2-methoxydiphenyl ether-5 : 4'-dicarboxylic acid; the free hydroxyl group of fangchinoline is therefore in an *iso*quinoline ring.[63]

Steroid and Polyterpenoid Bases.—H. Rochelmeyer [64] proposes to rename solanines *t* and *s* solatunine and solasonine, and the respective aglycones solatubine and solasodine; solancarpidine is identical with the last-named substance. Solasodine,[64] now found to be $C_{27}H_{43}O_2N$, yields *cyclo*pentenophenanthrene on fusion with selen-

[63] C. K. Chuang, C. Y. Hsing, Y. S. Kao, and K. J. Chang, *Ber.*, 1939, **72,** 519.

[64] H. Rochelmeyer, *Arch. Pharm.*, 1937, **275,** 336; H. Rochelmeyer and H. Chen, *ibid.*, 1939, **277,** 329; L. H. Briggs, *Nature*, 1939, **144,** 247.

ium, gives sterol colour reactions, and is precipitated by digitonin. It thus contains a steroid system with hydroxyl in the *cis*-3-position;
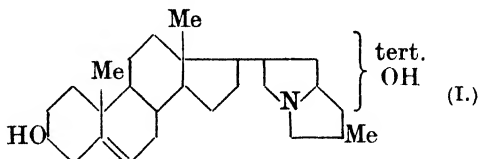
dehydration affords the solanosodine obtained along with solasodine from solasonine by previous workers. Two active hydrogen atoms are present, the nitrogen is tertiary and unmethylated; and solasodine is provisionally formulated as (I). A very similar formula had previously been proposed for solatubine,[65] which undergoes transformations analogous to those of sterols.[66]

Cevadine from *Veratrum sabadilla* is the tiglic ester of cevine, the degradation of which has been studied by W. A. Jacobs and L. C. Craig.[67] Energetic decompositions afforded a series of volatile bases, including 5-methyl-2-ethyl-pyridine and -piperidine, and a dicyclic tertiary base regarded as (II); coniine could not be identified.[68] Cevine methiodide yields a strongly alkaline base now believed to be a phenol- or enol-betaine. By distillation with soda–lime this gave a substance $C_8H_{15}(OH)(NMe)$ probably derived from 5-methyl-2-ethylpiperidine; Hofmann degradation appeared to give a cyclic ether. It is suggested that cevine may have the partial structure (III).
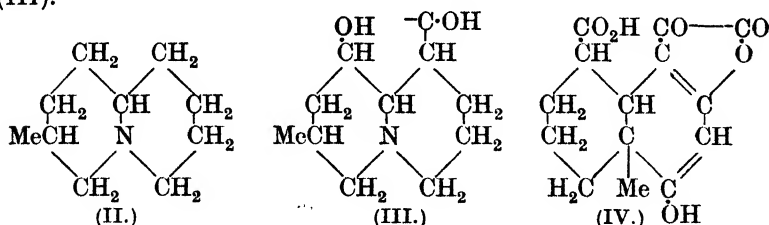
The oxidation of cevine throws some light on the nature of the remainder of the molecule, in which a benzphenanthrene system is already [69] indicated. An acid $C_{14}H_{14}O_6$ is obtained, termed decevinic acid, which is dehydrogenated by selenium to 2-hydroxynaphthalic anhydride. It is a lactonic acid giving the ferric chloride reaction

[65] G. R. Clemo, W. McG. Morgan, and R. Raper, *J.*, 1936, 1299.

[66] *Ann. Reports*, 1936, **33**, 378; H. Rochelmeyer, C. S. Shah, and E. Geyer, *Arch. Pharm.*, 1939, **277**, 340.

[67] *J. Biol. Chem.*, 1937, **119**, 141; **120**, 447; 1938, **124**, 659; **125**, 625; 1939, **129**, 79; 1940, **134**, 123; *J. Amer. Chem. Soc.*, 1939, **61**, 2252.

[68] Compare A. K. Macbeth and (Sir) R. Robinson, *J.*, 1922, **121**, 1571.

[69] *Ann. Reports*, 1936, **33**, 376.

of an enol; aqueous alkali adds a molecule of water and successively removes two of carbon dioxide, leading to a keto-lactone $C_{12}H_{16}O_3$. These and other reactions are interpreted by the tentative formula (IV) for decevinic acid.

Cassaine, isolated from *Erythophleum guineense*, is the dimethyl-aminoethyl ester of the mono-olefinic keto-hydroxy-acid cassaic acid, $C_{20}H_{30}O_4$. By reduction, followed by fusion with selenium, this gave 1 : 7 : 8-trimethylphenanthrene, and is hence a diterpenoid but probably not a steroid derivative.[70]

Strychnos Alkaloids.—The principal point against the most attractive variant (I) of Robinson's formula for strychnine was the ready bromination of diketonucidine (II); as such bromination does not after all take place, it is no longer necessary to attribute the grouping ·CO·ĊH· to diketonucidine.[71, 72] The transformations of strychnine and brucine have been discussed in detail in terms of the formula (I).[71]

Several papers have been devoted to the exhaustive methylation and Emde degradation of ψ-strychnine (I, with OH for H*) and ψ-brucine.[73] The results, which could be accommodated on the basis of (I) or the similar formula (III) of Leuchs, included disconcerting but intelligible transferences of methyl groups between oxygen and nitrogen :

[70] F. Faltis and L. Holzinger, *Ber.*, 1939, **72**, 1443; G. Dalma, *Helv. Chim. Acta*, 1939, **22**, 1497; L. Ruzicka and G. Dalma, *ibid.*, p. 1516.

[71] H. L. Holmes and (Sir) R. Robinson, *J.*, 1939, 603.

[72] H. Leuchs and H. Grunow, *Ber.*, 1939, **72**, 679; H. Leuchs, *ibid.*, p. 1588.

[73] H. Leuchs, *Ber.*, 1937, **70**, 2455; 1938, **71**, 660; H. Leuchs and K. Tessmar, *Ber.*, 1939, **72**, 965.

The Hofmann degradation of dihydrostrychnidine A (dihydro-I, with CH_2 for CO) has been carried to the point of elimination of N(b).[74] The complications arising from stereoisomerism and migration of double bonds can be interpreted by Robinson's or less easily by Leuchs's formula. Similar degradations have been effected in the brucidine and vomicidine series.[75]

ψ-Strychnine has been degraded to β-indolylethylamine derivatives,[76] and Leuchs has oxidised brucinonic acid to an acid formulated as (IV), in which only three of the alkaloid's seven rings survive.[77]

(IV.)

(V.)
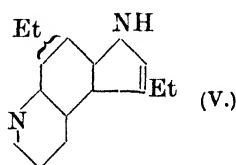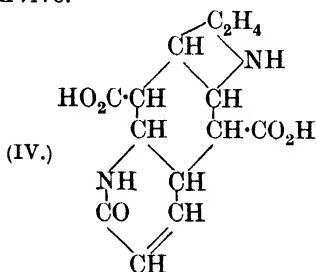
Vomipyrine, the degradation product $C_{15}H_{16}N_2$ of vomicine,[78] is not identical with either of the alternatives (V), both of which have been synthesised. Comparison of the absorption spectrum of vomipyrine with those of synthetic materials indicates, however, that the former must be a pyrroquinoline derivative.[79]

Pilosinine.—N. A. Preobrashenski, A. M. Poljakova, and V. A. Preobrashenski have synthesised *dl-iso*pilocarpine and -pilocarpine [80] by the method previously used for *d*-pilocarpine.[81] The same authors have prepared pilosinine (II) in the same way [82] from pilosinic acid (I), synthesised by heating ethyl itaconate :

(I.)   (II.)
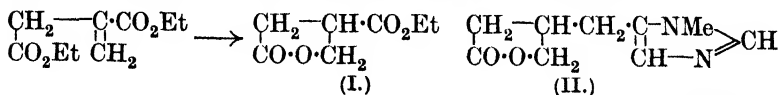
T. S. S.

[74] O. Achmatowicz and (Sir) R. Robinson, *J.*, 1938, 1467; O. Achmatowicz, *ibid.*, p. 1472; O. Achmatowicz and C. Dybowski, *ibid.*, p. 1483.

[75] *Idem, ibid.*, p. 1488; O. Achmatowicz and B. Racinski, *Rocz. Chem.*, 1938, **18**, 315.

[76] M. Kotake, T. Sakan, and S. Kusumoto, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1939, **35**, 415.

[77] *Ber.*, 1938, **71**, 2237.   [78] *Ann. Reports*, 1937, **34**, 367—8.

[79] H. Wieland and L. Horner, *Annalen*, 1938, **536**, 89; L. Horner, *ibid.*, 1939, **540**, 73.

[80] *Ber.*, 1936, **69**, 1314, 1835.   [81] *Ann. Reports*, 1935, **32**, 331.

[82] *J. Gen. Chem. Russia*, 1939, **9**, 1402.

BIOCHEMISTRY.

1. INTRODUCTION.

IN the course of comparatively a few years biochemistry has so developed that, from being a little-explored side-line of chemistry or physiology, it has become itself a vast new tract for investigation, with numerous sub-divisions of its own, each of which in turn forms the subject for intensive and specialised study by teams of researchers. Indeed so specialised have the various branches become that it is felt that the time is ripe to make a new departure with this issue of the *Annual Reports*, and to call in the aid of experts to deal with recent developments in their own lines of work.

Nutrition still accounts for by far the largest output of papers—no fewer than 5,127 abstracts are included in the year's list in *Nutrition Abstracts and Reviews*—and, following the custom of these Reports for a good many years past, it is accordingly placed first in order of attention. The increased importance of this subject in time of war needs no emphasis. Next follows an account, by J. R. Marrack, of some of the more remarkable of the recent findings in another field of equally great practical importance, namely immunochemistry. Still considering " the animal as a whole," we turn then to a discussion of the chemical control of the body through the agency of the secretions of the ductless glands. The number of such hormones already known exceeds that of the vitamins, and so with the restricted space at his disposal E. Kodicek has wisely limited his attention to one gland only, or a portion of it, namely, the anterior pituitary. Turning now, in a sense, from the needs of the whole animal to the chemistry of single components of its tissues, A. Neuberger deals with some significant recent advances in the study of nitrogenous substances, and J. F. Danielli reviews certain underlying physicochemical principles of concern to the biochemist. The enzymes are substances of such universal significance for all living tissues that an adequate understanding of their nature and their mode of action is a prime necessity for the advance of all aspects of biochemical knowledge; this field is covered by D. J. Bell in the section on biochemical catalysis. Leaving the animal kingdom behind, F. W. Norris, as in several recent years, contributes a section dealing in a general way with the chemical changes which occur in the living plant. A special aspect of this, glucoside formation, is then touched by R. Hill. Finally, coming to micro-organisms,

(Miss) M. Stephenson and E. F. Gale devote their section on bacterial biochemistry to two topics which have been much to the fore in recent literature, namely, " accessory food factors " and nitrogen metabolism.

L. J. H.

2. NUTRITION AND VITAMINS.

Vitamin A.

Human Requirements.—Interest has centred largely on the detection of deficiency by the dark-adaptation test [1] and the measurement of the daily human requirement for the vitamin. Estimates of the latter seem to work out in reasonably good agreement. In one particularly convincing experiment [2] ten volunteers were deprived of the vitamin for 188 days, until their visual sensitivity was 1/28 of the normal, and it was then ascertained that 2000—2500 I.U. of vitamin A, or 5000 I.U. of carotene, daily were the smallest amounts which would bring about a *slow* improvement in adaptation. No vitamin A was present in the blood until the dose of 2500 I.U. of vitamin A was reached or exceeded. The foregoing estimate errs perhaps in being on the low side, since there seems no doubt that larger intakes would be needed for a more prompt cure. L. E. Booher and E. C. Callison [3] found the requirement to be about 4000 and 7000 I.U. of carotene, given as cooked peas and cooked spinach respectively (recalculated to 70 kg. of body-weight); and W. v. Drigalski [4] considers that about 9800 I.U. of carotene daily are needed, increasing to about double or treble in lactation or late pregnancy.[5] H. R. Guilbert *et al.*,[6] after reviewing past data and comparing different mammalian species, cite 1400—4200 I.U. for vitamin A and 2800—14,000 I.U. for carotene, the former figure in each instance being the *minimum* for freedom from clinical symptoms, and the latter the *optimum* for normal adaptation, growth, and significant storage. Guilbert points out that the requirement for vitamin A remains relatively constant for a surprisingly large number of species, including the ox, sheep, pig, horse, and rat—namely, about 25 I.U. per kg. of body-weight for vitamin A, and about 50 I.U. for carotene. The differences between the vitamin and the " pro-vitamin " are of course due to the less complete absorption or assimilation of the latter, which may also

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[1] Compare *Ann. Reports*, 1939, **36**, 338.
[2] K. H. Wagner, *Z. physiol. Chem.*, 1940, **264**, 153.
[3] *J. Nutrition*, 1939, **18**, 459.
[4] *Klin. Woch.*, 1939, **18**, 1269.
[5] W. v. Drigalski and H. Kung, *ibid.*, p. 1318.
[6] H. R. Guilbert, C. E. Howell, and G. H. Hart, *J. Nutrition*, 1940, **19**, 91.

vary considerably according to the digestibility or the method used for cooking the vegetable containing the carotene.

Conditioned Deficiency in Man.—Several workers have confirmed that deficiency of vitamin A, as detected by the dark adaptation test, is commonly found in diseases of the liver (*e.g.*, cirrhosis, parenchymatous liver disease).[7, 8, 9] The deficiency runs parallel with the degree of damage of the liver,[8] and may be due either to inadequate absorption (as in obstructive jaundice and steatorrhœa), or to deficient storage caused by the hepatic dysfunction, and sometimes also to a lowered intake.[9] In juvenile diabetes dysadaptation is common, and the explanation is thought to be an inability to convert carotene into vitamin A.[10] Further indications have been given also of a frequent correlation between renal calculus and deficiency of vitamin A.[11]

Incidence of Deficiency.—Various investigators agree that dark adaptation tests give a reliable index of " partial deficiency," provided that the method is used with the proper precautions. G. Sankaran,[12] examining 600 convicts in a jail in Calcutta, found that 43% of the lower-class groups and 17% of the better-class groups showed a *high* degree of deficiency. This may be compared with the results of L. J. Harris and M. A. Abbasy,[13] who found a comparatively *mild* degree of deficiency present in about 30% of poor working-class children in England.

Tests for Deficiency in Man.—O. D. Abbott, C. F. Ahmann, and M. R. Overstreet [14] in U.S.A. and K. H. Wagner [2] in Germany point out that a differential leucocyte count is of value in diagnosing deficiency. Wagner found that after 188 days on a deficient diet the thrombocytes, too, were 70—85% below normal, and there was a leucopenia with a " right shift " of the differential count. Thus, four distinct criteria are now available for assessing deficiency in man : (1) dark adaptation, (2) the level of vitamin A in the blood, (3) presence of cornified cells in scrapings from the bulbar conjunctiva, (4) blood counts.

Experimental Avitaminosis A.—H. Mellanby [15] has recorded defects in the dental structure of young rats when their mothers'

[7] A. J. Patek and C. Haig, *J. Clin. Invest.*, 1939, **18**, 609.

[8] M. G. Wohl and J. B. Feldman, *J. Lab. Clin. Med.*, 1940, **25**, 485.

[9] M. Salah, *J. Egypt. Med. Assoc.*, 1940, **23**, 153.

[10] J. G. Brazer and A. C. Curtis, *Arch. intern. Med.*, 1940, **65**, 90; cf. also *J. Clin. Invest.*, 1939, **18**, 495.

[11] H. Long and L. N. Pyrah, *Brit. J. Urol.*, 1939, 216.

[12] Ann. Report All-India Inst. Hygiene and Pub. Hlth., Calcutta, 1939, p. 33.

[13] *Lancet*, 1939, ii, 1299, 1355.   [14] *Amer. J. Physiol.*, 1939, **126**, 254.

[15] *Brit. Dental J.*, 1939, **67**, 187.

diets were lacking in vitamin A. These include degenerated enamel organs, poorly calcified dentine, ossifying cells in pulp, abnormalities in the mandible. According to M. E. Sauer,[16] the epithelial metaplasia of avitaminosis A is independent of any nerve change. C. A. Baumann and T. Moore [17] have been unable to confirm the theory of a specific antagonism between thyroxin and vitamin A.

Workers in dietetics will have noted with interest that the so-called " light-white casein," frequently used in nutritional experiments, is contaminated with appreciable amounts of vitamin A ; [18] also that the disproportionately high values suggested for cheese have not been confirmed.[19] Reference must be made to a valuable review [20] covering both chemical and physiological aspects of carotene and related pigments.

Vitamin B_1.

Vitamin B_1 and the Pyruvate Oxidation System.—It is becoming clear that the system by which pyruvic acid is oxidised, under the influence of vitamin B_1 (as its pyrophosphate ester, cocarboxylase), may vary in some of its details from one tissue to another. In brain, or kidney cortex, C_4 dicarboxylates (*e.g.*, succinate and fumarate) seem to be of importance, and other components of the system include inorganic phosphate, Mg^{++} (or Mn^{++}), adenine nucleotide and probably cozymase (pyridine nucleotide).[21] In pigeon breast muscle [22] or liver,[23] on the other hand, the reaction appears to proceed through the citric acid cycle—*i.e.*, citric acid is formed as an intermediate—and among the principal products formed may be acetoacetate and α-ketoglutarate. The last-mentioned substance has been identified in large amounts in the urine of deficient rats,[24] and the quantity of citric acid is said to rise steeply shortly after a cure.[25]

An interesting development has followed the discovery of H. G. Wood and C. H. Werkman [26] that " propionic-acid bacteria " absorb carbon dioxide. They suggested that the mechanism might involve the addition of carbon dioxide to pyruvate to give oxaloacetate. H. A. Krebs and L. V. Eggleston [27] have now propounded the

[16] *Anat. Rec.*, 1939, **74**, 223.　　　　[17] *Biochem. J.*, 1939, **33**, 1639.

[18] M. K. Maitra and T. Moore, *ibid.*, p. 1648.

[19] A. W. Davies and T. Moore, *ibid.*, p. 1645.

[20] R. A. Morton, *Chem. and Ind.*, 1940, **59**, 301.

[21] I. Banga, S. Ochoa, and R. A. Peters, *Biochem. J.*, 1939, **33**, 1980.

[22] H. A. Krebs and L. V. Eggleston, *ibid.*, 1940, **34**, 442.

[23] E. A. Evans, *ibid.*, p. 829.

[24] P. E. Simola, *Biochem. Z.*, 1939, **302**, 84.

[25] H. A. Sober, M. A. Lipton, and C. A. Elvehjem, *J. Biol. Chem.*, 1940, **134**, 605.

[26] *Biochem. J.*, 1938, **32**, 1262; 1940, **34**, 7, 129.　　　[27] *Ibid.*, p. 1383.

hypothesis that in certain animal tissues, *e.g.*, in liver, and in bacteria, the vitamin is concerned not in the direct oxidation of pyruvate as hitherto supposed but in a preliminary carboxylation, analogous with the decarboxylation known to occur in yeast. This carboxylation results in the formation of oxaloacetate, and the latter then passes through the citric acid cycle, as follows :

(1) Carbon dioxide $+$ pyruvate $\longrightarrow$ oxaloacetate ;

(2) 2Oxaloacetate $+$ pyruvate $\longrightarrow$ citrate $+$ (fumarate $\longleftrightarrow$ malate) $+$ carbon dioxide ;

(3) Citrate $+$ oxaloacetate $\longrightarrow$ α-ketoglutarate $+$ (fumarate $\longleftrightarrow$ malate) $+$ carbon dioxide ;

the net result being the production of α-ketoglutarate plus fumarate in equilibrium with oxalate, according to the following equation :

(4) 4Pyruvate $+$ carbon dioxide $\longrightarrow$ α-ketoglutarate $+$ 2(fumarate $\longleftrightarrow$ malate).

However, this scheme does not appear to be of universal applicability ; for example, these reactions do not occur in brain.

There can be no doubt that the interconnections between pyruvate oxidation and other related systems are most complicated. For example, P. J. G. Mann and J. H. Quastel [28] have shown that the production of acetylcholine from pyruvate is increased when vitamin B_1 is added to an aerobic preparation of polyneuritic brain. A further example of the complexity of the system is the finding that the oxidation of acetate by bacteria requires the participation of the vitamin.[28a] Again, the observation [29] that insulin, like vitamin B_1, is able to lower the level of pyruvate in normal human blood suggests that the glycogen–glucose equilibrium and glucosemonophosphate formation are connected, if only indirectly, with the conversion of pyruvic acid.

Vitamin B_1 and Phosphorylating Mechanisms.—It is now clearly established that a cycle of phosphorylation accompanies the enzymic oxidation of pyruvate. In a preparation of brain, the rôle of adenylic acid seems to be to carry phosphate to hexosemonophosphate to form hexosediphosphate.[30] Phosphoglyceric and phosphopyruvic acids may have similar functions.[21] F. Lipmann's experiments [31] with *B. delbrückii* suggest that the unstable acetyl phosphate may be an intermediate phosphorylated derivative in the oxidation of pyruvic acid. As is well known, vitamin B_1 itself becomes phosphorylated in

[28] *Nature*, 1940, **145**, 856.

[28a] J. H. Quastel and D. M. Webley, *ibid.*, 1939, **144**, 633.

[29] H. v. Euler and B. Högberg, *Naturwiss.*, 1940, **28**, 29.

[30] S. Ochoa, *Nature*, 1940, **145**, 747; ·cf. also **146**, 267.

[31] *J. Biol. Chem.*, 1940, **134**, 463.

the organism to form the biologically active cocarboxylase, and according to H. Weil-Malherbe [32] it does so through the agency of adenine pyrophosphate; phosphoglyceric acid [33] also may accelerate the action.

Activation of Cocarboxylase by Free Vitamin B_1.—Some two years ago S. Ochoa [34] made the surprising observation that cocarboxylase activity is stimulated by the presence of free vitamin B_1. An elegant piece of work by H. G. K. Westenbrink and D. A. van Dorp [35] has now proved that the aneurin does this by inhibiting the hydrolysis of cocarboxylase by the phosphatases present in the tissue juices—*i.e.*, as a product of the reaction, it slows the net rate of the reaction.

Assessment of the Level of Nutrition.—The suggestion was made by G. G. Banerji and L. J. Harris [36] that the diminished tolerance towards the intermediates of carbohydrate metabolism observed in vitamin B_1 deficiency could be used as a test for assessing the level of nutrition. In rats the urinary excretion of pyruvate, or its level in the blood, is proportional to the degree of the deficiency; and this finding has been confirmed by other workers.[37] For detecting partial deficiencies in man, the procedure is slightly less simple, since it involves loading with test doses of glucose or pyruvate or other products of intermediate metabolism, followed by examination for the accumulation of abnormal amounts of such metabolites as pyruvic acid or α-ketoglutaric acid : the precise experimental details are still in process of being worked out.[36, 38] An alternative technique is the direct determination of the vitamin in urine,[39] and this method has been carefully standardised by Y. L. Wang and J. Yudkin,[40] who have also calculated from their data the probable human requirements. Alternatively, vitamin B_1, or cocarboxylase, can be measured in the blood.[41, 42]

[32] *Biochem. J.*, 1939, **33**, 1997.

[33] M. A. Lipton and C. A. Elvehjem, *Nature*, 1940, **145**, 226.

[34] *Ibid.*, 1938, **141**, 831 ; see also S. Ochoa and R. A. Peters, *Biochem. J.*, 1938, **32**, 1501.

[35] *Nature*, 1940, **145**, 465.

[36] *Chem. and Ind.*, 1939, **57**, 1190; *Biochem. J.*, 1939, **33**, 1346.

[37] M. Shils, H. G. Day, and E. V. McCollum, *Science*, 1940, **91**, 341; H. v. Euler and B. Högberg, *Naturwiss.*, 1939, **27**, 769.

[38] G. G. Banerji, *Biochem. J.*, 1940, **34**, 1329; see pp. 1332—1333; K. O. Elsom, F. D. W. Lukens, E. H. Montgomery, and L. Jonas, *J. Clin. Invest.*, 1940, **19**, 153; W. D. Robinson, D. Melnick, and H. Field, *ibid.*, p. 483.

[39] L. J. Harris and P. C. Leong, *Lancet*, 1936, i, 886; L. J. Harris, P. C. Leong, and C. C. Ungley, *ibid.*, 1938, i, 539; Y. L. Wang and L. J. Harris, *Biochem. J.*, 1939, **33**, 1356.

[40] *Ibid.*, 1940, **34**, 343.

[41] R. Goodhart and H. M. Sinclair, *J. Biol. Chem.*, 1940, **132**, 11.

[42] R. Goodhart, *ibid.*, 1940, **135**, 77.

Methods of Assay.—The bradycardia method [43] has been used for large-scale surveys of foodstuffs, in the East Indies, China, and elsewhere, and found to agree with various other methods (rat growth, rice-bird, colorimetric-diazo, etc.).[44] R. Goodhart [42] has recorded modifications in Sinclair and Goodhart's method for cocarboxylase in blood, H. M. Sinclair [45] in the Schopfer–Meiklejohn " fungus " test for B_1 in blood, and H. G. K. Westenbrink [46] in the Ochoa–Peters reaction for B_1 and cocarboxylase in yeast.

Vitamin-B_2 Complex.

Nicotinic Acid (Pellagra-preventive Factor).—E. Kodicek [47] has made a valuable study of the method for estimating nicotinic acid with *p*-aminoacetophenone.[47a]   Both he and W. R. Aykroyd and M. Swaminathan [48] have compared the distribution of the vitamin in various cereals and draw attention to the rather surprising fact that rice and millet may have little or no greater activity than maize, notwithstanding the well-known association of the latter with pellagra. In keeping with the known physiological function of nicotinic acid as a constituent of the pyridine coenzymes (phosphopyridine nucleotides), it has been proved that a deficiency, in either dogs or pigs, causes a fall in the amount of coenzyme I in their livers and muscles.[49]   The so-called Factor V (needed for cultivation of *Hæmophilus parainfluenzæ,* and served by either the di- or triphosphopyridine nucleotides) is similarly said to be lowered in the livers and muscles—but not in other tissues—of deficient dogs.[50] Human erythrocytes are able to synthesise Factor V *in vitro* when incubated with the vitamin, or *in vivo* when the latter is ingested by mouth.[51]   The biochemical rôle of the pyridine and other coenzymes has been much studied (see, for example, M. Dixon and L. G. Zerfas [52]), and is discussed more fully elsewhere in this Report

[43] T. W. Birch and L. J. Harris, *Biochem. J.,* 1934, **28,** 602 ; cf. *Ann. Reports,* 1939, **36,** 340.

[44] S. J. E. Pannekoek-Westenburg and A. G. van Veen, *Geneesk. Tijdschr. Nederl.-Indië,* 1939, **79,** 2891 ; E. F. Yang and B. S. Platt, *Chinese J. Physiol.,* 1939, **14,** 259 ; *A.,* 1940, III, 233 ; cf. also D. G. H. MacDonald and E. W McHenry, *Amer. J. Physiol.,* 1940, **128,** 608.

[45] *Biochem. J.,* 1939, **33,** 2027.

[46] *Enzymologia,* 1940, **8,** 97.

[47] *Biochem. J.,* 1940, **34,** 712, 724.

[47a] L. J. Harris and W. D. Raymond, *ibid.,* 1939, **33,** 2037.

[48] *Indian J. Med. Res.,* 1940, **27,** 667.

[49] A. E. Axelrod, R. J. Madden, and C. A. Elvehjem, *J. Biol. Chem.,* 1939, **131,** 85.

[50] H. I. Kohn, J. R. Klein, and W. J. Dann, *Biochem. J.,* 1939, **33,** 1432 ; M. Pittman and H. F. Fraser, *Publ. Health Reps., Wash.,* 1940, **55,** 915.

[51] H. I. Kohn and J. R. Klein, *J. Biol. Chem.,* 1940, **135,** 685.

[52] *Biochem. J.,* 1940, **34,** 371.

(see p. 415) and in a recent review by J. H. Quastel.[52a] Of clinical importance is the suggested use of nicotinic acid for treatment of Vincent's disease (trench mouth),[53] in sulphanilamide poisoning,[54] and in the so-called " encephalopathic syndrome." [55]

Riboflavin.—Deficiency of riboflavin in man is marked not only by lesions of the lips and seborrhœic accumulations on the face,[56] but by ocular manifestations, particularly photophobia and keratitis. These corneal lesions can be cured or made to reappear at will by administering or withholding riboflavin.[57] Similarly in rats, in addition to the skin lesions,[58] ocular symptoms are prominent : in order of onset these comprise conjunctivitis, blepharitis, corneal opacity, vascularisation and ulceration of the cornea, and finally cataract. All except the cataract are cured by riboflavin without any other treatment.[59] Flavin is important, likewise, in the rearing of pigs [60] and poultry.[61] A method for checking the biological activity of various flavins, using lactic acid bacteria, has been described.[62]

Pantothenic Acid (Chick-pellagra Factor, Filtrate Factor).—The structure of pantothenic acid has now been settled.[63] The synthetic dextrorotatory compound [64, 65, 66] has been tested on micro-organisms, on chicks and on rats and found to have the identical activity of the naturally occurring substance : [65, 67] the racemic acid has 50% of the

[52a] Lecture delivered before the Institute of Chemistry of Great Britain and Ireland, 4th October, 1940.

[53] J. D. King, *Lancet*, 1940, **2**, 32.

[54] J. F. Doughty, *J. Amer. Med. Assoc.*, 1940, **114**, 756 ; G. B. Cottini, *Dermatologica*, 1940, **81**, 83.

[55] N. Jolliffe, *Res. Publn. Ass. nerv. ment. Dis.*, 1939, **19**, 148 ; N. Jolliffe, K. M. Bowman, L. A. Rosenblum, and H. D. Fein, *J. Amer. Med. Assoc.*, 1940, **114**, 307.

[56] W. H. Sebrell and R. E. Butler, *Publ. Health Reps.*, *Wash.*, 1939, **54**, 2121 ; N. Jolliffe, H. D. Fein, and L. A. Rosenblum, *New Engl. J. Med.*, 1939, **221**, 921.

[57] H. D. Kruse, V. P. Sydenstricker, W. H. Sebrell, and H. M. Cleckley, *Publ. Health Reps.*, *Wash.*, 1940, **55**, 157.

[58] H. Chick, T. F. Macrae, and A. N. Worden, *Biochem. J.*, 1940, **34**, 580.

[59] M. M. El-Sadr, *Chem. and Ind.*, 1939, **58**, 1020.

[60] E. H. Hughes, *J. Nutrition*, 1940, **20**, 233.

[61] A. E. Schumacher and C. F. Heuser, *Poultry Sci.*, 1939, **18**, 369.

[62] E. E. Snell and F. M. Strong, *Enzymologia*, 1939, **6**, 186 ; R. E. Feeney and F. M. Strong, *J. Biol. Chem.*, 1940, **133**, proc. xxxi.

[63] See this vol., p. 226.

[64] R. J. Williams, H. K. Mitchell, H. H. Weinstock, and E. E. Snell, *J. Amer. Chem. Soc.*, 1940, **62**, 1784.

[65] E. T. Stiller, S. A. Harris, J. Finkelstein, J. C. Keresztesy, and K. Folkers, *ibid.*, p. 1785.

[66] D. W. Woolley, *ibid.*, p. 2251.

[67] H. H. Weinstock, A. Arnold, E. L. May, and D. Price, *Science*, 1940, **91**, 411 ; S. H. Babcock and T. H. Jukes, *J. Amer. Chem. Soc.*, 1940, **62**, 1628.

activity, and (—)pantothenic acid is inactive;[65] the hydroxy-derivative[68] has a variable potency depending on conditions, but various other synthetic analogues are biologically inert.[69]

The pathological and physiological relations of pantothenic acid are now receiving attention. In chicks,[70] a deficiency results in degeneration of the nerve fibres of the spinal cord. In rats,[71] as well as the better known symptoms[58] such as nose bleeding, sticky exudate on eyelids, and depilation about the nose, the adrenals are said to suffer hæmorrhage, atrophy, and necrosis. The tissues of deficient chicks have been shown to be low in the vitamin;[72] and a method has been suggested for estimating it in human blood.[73]

The conclusion given in last year's Report about the identity of the " filtrate factor," needed by rats, with pantothenic acid has been further confirmed.[74] Associated with the filtrate factor are other substances also needed by rats, viz., the so-called β- and γ-factors of the British workers[74] and the Factor W of Elvehjem and his collaborators.[75]

Vitamin C.

Deficiency in Man.—Working details have been given of the simplified procedure for assessing the level of nutrition of vitamin C in human subjects, by means of the urine test : controls at a home for waifs and strays in Cambridge where an orange was provided daily were found to be up to standard, whereas in poor-class homes in the same town some 40% of the children were " below standard " and 5% had a relatively severe deficiency.[76] When it is merely desired to distinguish in a rough qualitative way between children with high and with low " reserves," it is possible to use a still simpler modification of the test.[77] In polar regions, the large consumption of fresh meat, and at some seasons of arctic flora, generally keeps the

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[68] H. K. Mitchell, E. E. Snell, and R. J. Williams, *J. Amer. Chem. Soc.*, 1940, **62,** 1791.

[69] H. H. Weinstock, E. L. May, A. Arnold, and D. Price, *J. Biol. Chem.*, 1940, **135,** 343.

[70] P. H. Phillips and R. W. Engel, *J. Nutrition*, 1939, **18,** 227; quoted by *Brit. Med. J.*, 1940, **2,** 230.

[71] F. S. Daft, W. H. Sebrell, S. H. Babcock, and T. H. Jukes, *Publ. Health Reps., Wash.*, 1940, **55,** 1333; L. L. Ashburn, *ibid.*, p. 1337.

[72] E. E. Snell, D. Pennington, and R. J. Williams, *J. Biol. Chem.*, 1940, **133,** 559.

[73] S. R. Stanbery, E. E. Snell, and T. D. Spies, *ibid.*, 1940, **135,** 353.

[74] B. Lythgoe, T. F. Macrae, R. H. Stanley, A. R. Todd, and C. E. Work, *Biochem. J.*, 1940, **34,** 1335.

[75] S. Black, D. V. Frost, and C. A. Elvehjem, *J. Biol. Chem.*, 1940, **132,** 65; J. J. Oleson and S. Black, *ibid.*, 1940, **133,** proc. lxxiii.

[76] L. J. Harris, *Lancet*, 1940, ii, 259.

[77] J. Pemberton, *Brit. Med. J.*, 1940, **2,** 217.

people free from scurvy,[78] but certain Eskimos on a diet devoid of meat were found to be deficient in the vitamin when tested either for the ascorbic acid in their blood or for capillary resistance—both could be improved if orange juice were given.[79]   Other signs of deficiency included rhinitis, œdematous nasal mucous membranes, epistaxis and increased severity of the cutaneous response to tuberculin.[79, 80]   The increased importance of an adequate supply of vitamin C in war-time is illustrated by the fact that the healing of wounds and the formation of callus are delayed by partial deficiencies.[81]   Those working on the apparent connection between vitamin C and resistance to infection may receive further clues from the observation concerning the tuberculin reaction mentioned above, and from the finding of the workers at Pittsburg that the administration of hypnotics such as barbiturates or chloretone caused an increased synthesis of the vitamin by rats, attributable, it is presumed, to its connection with detoxication processes.[82]

Properties and Distribution of Ascorbic Acid.—A valuable compilation has been made by M. Olliver [83] of the distribution of vitamin C in numerous raw and cooked fruits and vegetables.   C. L. Arcus and S. S. Zilva [84] have examined the photochemical decomposition of ascorbic acid and conclude that " it is improbable that any ultra-violet light penetrating superficial tissues containing *l*-ascorbic acid would bring about the oxidation of the vitamin *in vivo*."

Other Vitamins.

Owing to lack of space this year, a discussion of recent work on vitamins D and E will have to be postponed until the next volume.

Vitamin K.—The formula given provisionally for vitamin K_2 in

Vitamin K₂
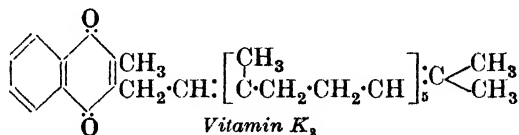
last year's Report has been modified.   Instead of two farnesyl residues, one each in the 2- and the 3-position, it is now thought that

[78] K. Rodahl, private communication.

[79] V. E. Levine, *J. Biol. Chem.*, 1940, **133**, proc. lxi.

[80] A. Høygaard, *Nord. med. Tidsskr.*, 1938, **16**, 1647.   For further reference to the tuberculin reaction in vitamin C deficiency, see also K. M. Birkhaug, *Acta tuberc. Scand.*, 1939, **13**, 45; quoted by V. E. Levine (*loc. cit.*).

[81] E. W. Lexer, *Arch. klin. Chir.*, 1939, **195**, 611.

[82] H. E. Longenecker, H. H. Fricke, and C. G. King, *J. Biol. Chem.*, 1940, **135**, 497.

[83] *Lancet*, 1940, ii, 190.

[84] *Biochem. J.*, 1940, **34**, 61.

the two are combined, joined head to tail, in the 3-position.[85] According to this view vitamin K_2 is 3-difarnesyl-2-methyl-1 : 4-naphthaquinone. This brings K_2 into line with all the more potent K-factors, in having a methyl substituent in the 2-position.

" *Vitamin P*."—The claims for " vitamin P " have again been controverted, so far as concerns the guinea pig; [86] for the human some clinical observers record positive [87] and others negative results.[88] We may reasonably hope for an explanation of the discrepancy within a year or two.

Vitamin F (Essential Unsaturated Fatty Acids).—The previous indications given by T. W. Birch and his co-workers of inter-relations between vitamin B_6 and the nutritionally essential fatty acids have been confirmed : symptoms of so-called acrodynia in the rat may, it seems, be cured by either factor independently.[89] Possibly, however, the symptoms in the two deficiencies are similar but not identical; indeed G. O. Burr, J. B. Brown, and W. O. Lundberg [90] say that the unsaturated fatty acids themselves (linolenic, linoleic, arachidonic, etc.) should not be treated as an interchangeable group, since they differ appreciably in their effects on growth and on the skin lesions. Interesting studies of the relative potencies of various esters of these fatty acids, and of their effects on fat metabolism, have been made by (Mrs.) I. Smedley-Maclean and her colleagues at the Lister Institute.[91]

Vitamin H.—Vitamin H is the substance which protects rats against " egg-white injury," that is to say, against the symptoms produced by consumption of large amounts of raw or of insufficiently cooked egg-white.[91a] Investigations on this vitamin were begun by P. György in Heidelberg in 1927, were resumed with T. W. Birch in Cambridge from 1933—1935, and have since been continued in conjunction with others in America. A full resumé of all these extended experiments has appeared.[92] One of the most interesting

[85] S. B. Binkley, R. W. McKee, S. A. Thayer, and E. A. Doisy, *J. Biol. Chem.*, 1940, **133**, 721.

[86] L. E. Detrick, M. S. Dunn, W. L. McNamara, and N. E. Hubbard, *J. Lab. Clin. Med.*, 1940, **25**, 684.

[87] H. Scarborough, *Biochem. J.*, 1939, **33**, 1400; *Lancet*, 1940, ii, 644; D. R. Gorrie, *ibid.*, i, 1005.

[88] *E.g.*, E. Davis, *ibid.*, p. 1062.

[89] H. Schneider, H. Steenbock, and B. R. Platz, *J. Biol. Chem.*, 1940, **132**, 539.

[90] *Proc. Soc. Exp. Biol. Med.*, 1940, **44**, 242.

[91] E. M. Hume, L. C. A. Nunn, I. Smedley-MacLean, and H. H. Smith, *Biochem. J.*, 1940, **34**, 879; I. Smedley-MacLean and L. C. A. Nunn, *ibid.*, p. 884; G. C. Hevesy and I. Smedley-MacLean, *ibid.*, p. 903.

[91a] M. A. Boas, *ibid.*, 1927, **21**, 712.

[92] P. György, *J. Biol. Chem.*, 1939, **131**, 733; P. György, R. Kuhn, and E. Lederer, *ibid.*, p. 745; T. W. Birch and P. György, *ibid.*, p. 761.

points is that vitamin H as it occurs in yeast or liver is insoluble in water or fats, but can be made soluble in water by autolysis (in the case of yeast) or by a suitable process of digestion (in the case of liver). It is three to five times more effective when given parenterally than by mouth.[93] Lastly the important suggestion has been made that vitamin H is probably identical [94, 95] with biotin ("bios II B ")—a factor needed for the growth of yeast and by certain strains of *S. aureus*—and also with " Coenzyme R " [94]—a growth factor needed by nodular organisms in certain plant roots.

New Vitamins.—The casual reader of current literature on vitamins will probably be mystified by allusions to such novel terms as the grass-juice factor, the anti-grey-hair factor, vitamins L and M, etc. Most of these newly described substances are as yet but poorly characterised chemically, but for enumeration and classification reference may be had to a recent review.[96]

Nutrition in War-time.

In Britain the nutritional problem is, in essence, how to secure adequate nutrition while reducing the importation of food to the minimum. The solution lies, mainly, in an increased reliance on commodities already produced in large quantities at home. Potatoes and milk come foremost in this category. Together these two foods constitute a regimen which is not far from complete as regards most of the vitamins, mineral salts, and protein; and enough of each is available to furnish a considerable proportion of the daily food requirements of the population.[97] Examples of two other home-produced foodstuffs which are being encouraged are carrots, valuable as a source of vitamin A, and oatmeal, also a native crop and good for cheap calories and for vitamin B_1. The " nutrition front " must be of supreme interest to every chemist and biochemist just now, as an instance where applied chemical and biochemical knowledge has become of fundamental importance to the national life. The theme, unfortunately, cannot be more than vaguely outlined here, and we must content ourselves with a cross reference to some more detailed recent writings.[98]

[93] P. György and C. S. Rose, *Proc. Soc. Exp. Biol. Med.*, 1940, **43**, 73.

[94] P. György, D. B. Melville, D. Burk, and V. du Vigneaud, *Science*, 1940, **91**, 243.

[95] J. R. Porter and M. J. Pelczar, *ibid.*, p. 576.

[96] L. J. Harris, *Post Grad. Med. J.*, 1941, **17**, 34.

[97] For discussion on the potato as a war-time food, see R. N. Salaman and others in contributions to a symposium reported in *Chem. and Ind.*, 1940, **59**, 735 *et seq.*

[98] *E.g.*, Sir J. B. Orr and D. Lubbock, " Feeding the People in War-Time," 1940; L. J. Harris, *Practitioner*, 1940, **145**, 105; J. C. Drummond, Sir R.

White versus Brown Bread.—Nutrition workers are unanimous in recognising wholemeal flour, or flour of a similar high degree of " extraction," as superior to white flour. The proposal to fortify white bread by adding to it crystalline aneurin plus a calcium salt, stated to be the carbonate, has been discussed by many authors.[99, 100] The addition of vitamin B_1 and calcium does not, however, make good all the deficiencies of white flour as compared with wheatmeal, and this has been convincingly confirmed in growth tests on rats by H. Chick.[101]   L. J. H.

3. Immunochemistry.

Bacterial Antigens.

G. G. Freeman, S. W. Challinor, and J. Wilson [1] have compared the antigens isolated from members of the *Salmonella* group (*Bact. Typhi-murium* and *Bact. Typhosus*) by the methods of A. Boivin and L. Mesrobeanu,[2] and R. Raistrick and W. W. C. Topley [3] and by extraction with ethylene glycol and diethylene glycol.[4] They also prepared the antigens from bacteria grown on a synthetic medium. J. Walker [5] used a method of extraction with concentrated solutions of urea. The four methods gave very similar products. G. M. Mackenzie, R. H. Pike, and R. E. Swinney [6] also found that similar products were obtained by the methods of Raistrick and Topley and of Boivin and Mesrobeanu. It may be supposed that the antigenic material obtained by these diverse methods exists as a complex in the bacteria and is not a chance mixture of various contents of the bacterial cell and the culture made.

Morgan [4] extracted from *Bact. Dysenteriæ* (Shiga) an antigen

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McCarrison, Sir J. B. Orr, Sir F. Keeble, L. H. Lampitt, V. H. Mottram, J. C. Spence, and F. Kidd, " The Nation's Larder . . .," 1940; G. Bourne, " Nutrition and the War," 1940; Sir J. Russell, *Nature*, 1940, **145**, 11. See also the valuable tabulations by A. L. Bacharach and J. C. Drummond, *Chem. and Ind.*, 1940, **59**, 37, on the human requirements for vitamins, expressed both as marginal and as optimal limits, and by A. L. Bacharach, *Food*, 1940, **9**, 110, on the contributions made by the more important foodstuffs towards these requirements.

[99] *E.g.*, Accessory Food Factors Committee, *Lancet*, 1940, ii, 143; W. C. McCulloch, *Brit. Med., J.,* 1940, **2**, 397; J. P. McGowan, *ibid.*, p. 398; (Sir) E. Graham-Little, *Lancet*, 1940, ii, 311; A. L. Bacharach, *Food Manufacture*, 1940, **15**, 220; E. R. Dawson, *Chem. and Ind.*, 1940, **59**, 784.

[100] T. Moran and J. C. Drummond, *Nature*, 1940, **146**, 117.

[101] *Lancet*, 1940, ii, 511.   [1] *Biochem. J.*, 1940, **34**, 307.

[2] *Compt. rend. Soc. Biol.*, 1933, **112**, 76.

[3] *Brit. J. Exp. Path.*, 1934, **15**, 114.

[4] W. T. J. Morgan, *Biochem. J.*, 1937, **31**, 2503.

[5] *Ibid.*, 1940, **34**, 325.   [6] *J. Bact.*, 1940, **40**, 197.

(ABC) composed of a phospholipin (A), a polysaccharide (B), and a polypeptide (C). W. T. J. Morgan and S. J. Partridge [7] consider that the product is a homogeneous complex, which can induce the formation of antibodies like the intact organism. If A is removed, BC is still antigenic (induces formation of antibodies on injection), but A alone and AB are not. C on injection into rabbits gives rise to antibodies that react with C or BC; however, these do not appear to be the same as those evoked by BC or the intact organism. BC can be regenerated from isolated B and C. The purified polysaccharide B forms precipitates with antisera to the bacteria.

To obtain a bacterial antigen with the minimum disintegration A. A. Miles and N. W. Pirie [8] extracted *Br. Melitensis* with chloroform water. They obtained a substance [PLAPS], from which a phospholipin PL, and a protein-like substance S could be successively removed, leaving AP. Hydrolysis with weak hydrochloric acid split AP, liberating a phospholipin and an N-formylated amino-polyhydroxide compound A, which may be a formylated amino-hexose. [PLAPS], which forms viscous opalescent solutions that show anisotropy of flow, is split on treatment with sodium dodecyl sulphate into smaller particles, PLAPS, with molecular weights between 10^5 and 10^6. AP has a molecular weight of about 10^6, which can be reduced to between 1 and 2×10^5. The amine, freed from formic acid, is fairly homogeneous,[9] with a minimum particle weight of 3300.

The ability to form antibodies on injection (antigenicity) is in the order [PLAPS] > PLAPS > AP; the antigenicity of AP may be due to contamination with traces of PLAPS. [PLAPS] forms more precipitate with antisera than PLAPS or AP. A is not antigenic and forms no precipitate with antisera. These substances, when added in excess, inhibit the agglutination of *Br. Melitensis* by homologous antisera. The concentrations required for inhibition are in the order Free amine $\gg$ A > [PLAPS] > AP.

These observations illustrate with single natural antigens the dependence of antigenicity and the formation of precipitates with antisera on the degree of aggregation and complexity of the complex, and of the specificity on a relatively simple fraction of the antigen.

Natural Protein Antigens.

Catalase.—Antisera to crystalline ox catalase have been obtained by immunising rabbits.[10] Dog and horse catalase also formed pre-

[7] *Biochem. J.*, 1940, **34**, 169.

[8] *Brit. J. Exp. Path.*, 1939, **20**, 83, 109, 278; *Biochem. J.*, 1939, **33**, 1709, 1716.

[9] J. St. L. Philpot, *Biochem. J.*, 1939, **33**, 728.

[10] D. A. Campbell and L. Fourt, *J. Biol. Chem.*, 1939, **129**, 383.

cipitates with the antiserum ; but hæmoglobin and hæmatin neither formed precipitates with the antiserum nor inhibited the formation of a precipitate by catalase and antiserum. The specificity of the catalase is, therefore, not determined by the iron–porphyrin group.

When the catalase was precipitated in combination with antibody, its enzyme activity was unimpaired; the specific groups that combine with antibody are not the same as those involved in the enzyme activity.

Bence Jones Proteins.—L. Hektoen and W. H. Welker [11] have confirmed conclusions from previous work that Bence Jones proteins fall into two groups, which are immunologically distinct. Both types may be excreted by the same patient. They report that Medes has found the nitrogen distribution similar in all but one of their preparations. The immunological behaviour of this one resembled that of other preparations from which it differed chemically. This suggests that the specificity of these proteins is determined by a small part of the protein molecule.

L. Pillemer and others [12] have studied the specificity of keratin derivatives. They find a difference between feather and wool keratin and consider that the $S \cdot C \cdot CO_2 H$ group is of prime importance in determining specificity.

Synthetic Antigens.

W. F. Goebel [13] has continued his investigations [14] on the rôle of uronic acids in the immunity to pneumococci. He found that synthetic antigens containing gentiobiuronic and cellobiuronic acids linked to horse serum globulin (GeA- and CA-globulin) evoked in rabbits antibodies which conferred passive immunity on mice against multiple doses of Type II pneumococci. However, antisera to GeA-globulin did not protect mice against Type III and Type VIII pneumococci, as did antisera to CA-globulin.[14] The specific polysaccharides of Type III and Type VIII pneumococci contain cellobiuronic acids ; the uronic acid constituent of Type II polysaccharide is still unknown. The cross reactions of GeA- and CA-globulins and of similar compounds containing gentiobiose were studied. The point of attachment of the glucose or glucuronic acid to the glucose seemed of more importance than the presence of a carboxyl group.

Further investigations have been made into the effects of substitution in the amino-group of proteins on their immunological behaviour. If the amino-group of a protein P_1 (*e.g.*, horse serum globulin) is treated to form $P_1 R$, will (1) $P_1 R$ still form a precipitate

[11] *Biochem. J.*, 1940, **34**, 487.   [12] *J. Exp. Med.*, 1939, **70**, 287.
[13] *Ibid.*, 1940, **72**, 33.   [14] *Ibid.*, 1939, **69**, 33.

with antisera to the untreated protein P_1, (2) P_1 form a precipitate with antisera to P_1R, (3) the product P_2R, formed with another protein P_2 (*e.g.*, egg albumin), form a precipitate with antisera to P_1R, and (4) the formation of a precipitate by P_2R and antisera to P_1R be inhibited by the relatively simple compounds (AR) formed by treating amino-groups of amino-acids ?

Formaldehyde Treatment (P_1F).—L. J. Jacobs and S. C. Gommers [15] compared the effects of the various methods of treatment with formaldehyde that have been used by previous workers. They found that P_1F formed precipitates with antisera to P_1, and P_1 with antisera to P_1F; P_2F formed little or no precipitate with antisera to P_1F.

A. B. Kleczkowski,[16] using quantitative methods in place of the traditional inspection and rows of + signs, found that P_1F precipitated all the antibody from antisera to P_1.

Phenylureidoproteins (PU).[17] Kleczkowski found that P_1U also precipitated all the antibody from antisera to P_1. P_2U precipitated only part of the antibody from antisera to P_1U, which did not react with P_1.

Diethyl sulphide and diethylsulphone proteins (PMS *and* PMSO). L. Berenblum and A. Wormall [18] treated horse serum globulin with $\beta\beta'$-dichlorodiethyl sulphide and $\beta\beta'$-dichlorodiethylsulphone, forming P_1MS and P_1MSO. P_1MS formed a slight precipitate with antisera to P_1, and P_1 with antisera to P_1MS. P_2MS and P_2MSO reacted weakly with antisera to P_1MS and P_1MSO respectively.

Carbobenzyloxyproteins (PC). P_2C formed precipitates with antisera to P_1C. This reaction was inhibited by carbobenzyloxy-glycine and the rather similar phenylureidoglycine.[19]

Aspirylproteins (PA). G. C. Butler, C. R. Harington, and M. E. Yuill (working with Miles) [20] found that P_2A reacted with antisera to P_1A; the reaction was inhibited by aspirylglycine and to a less degree by salicylglycine.

These experiments show that the specificity of proteins is little affected when the amino-group is changed by treatment with formaldehyde ; but that when larger groups are attached at this site, the specificity is altered. They suggest that the amino-groups have little relation to the immunological behaviour of proteins and that when a new specificity is introduced it is not due to loss of the free amino-group but to the presence of large new groups.

[15] *J. Immun.*, 1939, **36**, 531.   [16] *Brit. J. Exp. Path.*, 1940, **21**, 1.

[17] S. J. Hopkins and A. Wormall, *Biochem. J.*, 1933, **27**, 740; 1934, **28**, 228.

[18] *Ibid.*, 1939, **33**, 75.

[19] W. E. Gaunt and A. Wormall, *ibid.*, p. 908.

[20] *Ibid.*, 1940, **34**, 838.

According to A. B. Kleczkowski,[21] in the course of iodination of horse serum globulin the ability to react with and the ability to evoke antibodies to native globulin disappear when all the tyrosin is substituted.

Butler, Harington, and Yuill [20] also found that injection of antisera to P_1A reduced the antipyretic action of aspirin (compare a similar effect with thyroxin; *Chem. Reviews,* 1938, 356).

Antibodies.

The recognition that antibodies are modified serum globulins and the new methods of characterising proteins have led to considerable work on the physical properties of antibodies.   A. Tiselius [22] found that normal serum globulin consisted of three fractions, whose mobilities in an electric field at p_H between 7 and 8 were in the order $\alpha > \beta > \gamma$.   Horse antisera may contain either an excess of the γ-fraction or a new fraction, T, with a mobility between those of the β- and the γ-fraction.   When the antibody is removed by absorption with the corresponding antigen, the γ-fraction is reduced or the γ-fraction removed.   In the sera of men, monkeys, and rabbits, antibodies were found mainly in the γ-fraction.[22, 23, 24]

According to J. van der Scheer, R. W. G. Wyckoff, and F. H. Clarke [25] all horse antisera to toxins contain the new fraction T, whereas horse antisera to bacterial polysaccharides and proteins contain abnormal amounts of the γ-fraction.   Some antitoxic sera contain both T-fraction and excess of γ-fraction.   These authors suggest that these two fractions may contain antibodies to two different antigens present in the complex substance used for immunisation.   Pappenheimer, Lundgren, and Williams [39] also found that diphtheria antitoxin formed a new serum globulin fraction. However, Tiselius and Kabat [23] found that the antibody of horse antisera to pneumococcal polysaccharide was in the T-fraction, and N. Fell, W. G. Stern, and R. D. Coghill [26] found no abnormal fraction in antisera to various bacterial toxins.

Using the ultra-centrifuge, Biscoe, Hercik, and Wyckoff [24] and H. Heidelberger and K. O. Pedersen [27] showed that purified antibodies, from horse antisera to the pneumococcal polysaccharides, had very high sedimentation constants, whereas antibodies of rabbit antisera both to pneumococcal polysaccharides and to proteins had sedimentation constants close to those of normal serum globulin. E. A. Kabat [28] extended this work; he contrasted the antibodies

[21] *Brit. J. Exp. Path.,* 1940, **21**, 98.   [22] *Biochem. J.,* 1937, **31**, 1464.
[23] A. Tiselius and E. A. Kabat, *J. Exp. Med.,* 1939, **69**, 119.
[24] J. Biscoe, F. Hercik, and R. W. G. Wyckoff, *Science,* 1936, **83**, 602.
[25] *J. Immun.,* 1940, **39**, 65 (references are given to previous work).
[26] *Ibid.,* p. 223.   [27] *J. Exp. Med.,* 1937, **65**, 393.   [28] *Ibid.,* 1939, **69**, 103.

found in the sera of horses, cows, and pigs, which are very large (molecular weight about 990,000) and unsymmetrical, with those of the sera of men, monkeys, and rabbits which resemble normal serum globulin (molecular weight 157,000 to 195,000). A. M. Pappenheimer (jun.), H. P. Lundgren, and J. W. Williams,[29] however, found that the molecular weight of diphtheria antitoxin in horse serum is about 155,000 ; and Fell, Stern, and Coghill,[26] that horse antisera to various bacterial toxins contain no proteins of large molecular weight. Kabat [28] also found that, on prolonged immunisation of horses against pneumococci, smaller antibody molecules were formed. So that it seems that there is no inherent difference between antibodies either in molecular weight or in charge, dependent on the species in which they are formed or on the antigen with which they react.

Enzymic Digestion.—Quantitative experiments were made by A. M. Pappenheimer (jun.) and E. S. Robinson [30] with the diphtheria antitoxin prepared by the Parfentjev digestion process. These suggest that the antibody molecules are split by the enzyme into an active and an inactive part. Similar work by P. Grabar [31] indicates that the antibody to pneumococcal polysaccharides is split by pepsin into two approximately equal parts, one active and the other inactive. C. G. Pope [32] studied the effect of varying conditions, p_H, time of digestion, etc., on the purification of antibody by digestion with proteolytic enzymes. He finds that antibodies are readily split by digestion in a very short time into an inactive portion, which is easily denatured by heat, and an active portion more resistant to heat. Ordinary antitoxin contains 60,000—90,000 units, and enzyme-treated antitoxin about 140,000 units, per gram of protein (also found by Pappenheimer and Robinson). Continuation of this work would shed light on the structure of proteins and the peculiarities of the structure of antibodies.

The practical value of this method lies in the elimination of non-specific proteins, which make up some 90% of the proteins of an untreated serum. The results can be judged by the number of units of antitoxin per gram of protein in the product, which may be increased eight times. Various techniques depending on long digestion have proved less satisfactory.[33, 34, 35] Since the digested

[29] *J. Exp. Med.*, 1940, **71**, 247.   [30] *J. Immun.*, 1937, **32**, 291.

[31] *Ann. Inst. Pasteur*, 1938, **61**, 765.

[32] *Brit. J. Exp. Path.*, 1939, **20**, 132, 201, 213.

[33] F. Modern and G. Ruff, *Compt. rend. Soc. Biol.*, 1938, **129**, 851 ; *Biochem. Z.*, 1938, **299**, 377.

[34] F. Hansen, *Compt. rend. Soc. Biol.*, 1938, **129**, 216 ; *Biochem. Z.*, 1938, **299**, 363.

[35] G. Sandor, *Compt. rend. Soc. Biol.*, 1939, **130**, 840, 1187.

antibody appears not to be antigenic,[37] injection of it should not cause serum sickness or anaphylaxis, which, however, is a very rare accident in man.   The method can also be applied to tetanus antitoxin.[36]

The Reaction between Antibodies and Antigens.

Knowing the molecular weights of antibody (A) and antigen (G), it is possible to calculate the composition of the aggregate formed by their interaction; this has been done by M. Heidelberger [38] and A. M. Pappenheimer (jun.), H. P. Lundgren, and J. W. Williams.[39] Theories of the reaction between A and G suppose that large soluble aggregates are formed when G is in great excess.   The formation of such aggregates has been shown by the ultra-centrifuge.

The reactions of A and G when spread in films on surfaces have been studied.[40]   Measurements of the thickness of films on solid surfaces have given objective demonstration of the specific union of A and G, proof that a molecule of A can combine with more than one molecule of G, and vice versa, and dimensions of A and G molecules that agree fairly well with those obtained by other methods.   Some discrepancies may be due to unequal spreading and to the use of different methods of spreading and different types of surface.

When antibodies to the bacterial polysaccharides are spread on water to form a film, one amino-acid thick, they do not combine with the corresponding polysaccharides.   In films on solid surfaces, the antibodies preserve a " globular " form and combine with polysaccharide.   J. R. M.

4. HORMONES.

Since the anterior pituitary hormones have not been discussed in these Reports lately, this section will deal exclusively with the more important investigations on this gland, the consideration of other endocrine organs being kept over for later reports.   Even so, it is obviously impossible, in one brief section, to mention all contributions concerning this particular gland.

[36] G. Sandor and R. Richou, *Compt. rend. Soc. Biol.*, 1939, **131**, 461.

[37] A. J. Weil, I. A. Parfentjev, and K. L. Bowman, *J. Immun.*, 1938, **35**, 399.

[38] *J. Amer. Chem. Soc.*, 1938, **69**, 103.

[39] *J. Exp. Med.*, 1940, **71**, 247.

[40] I. Langmuir and V. J. Schaefer, *J. Amer. Chem. Soc.*, 1937, **59**, 1406; J. F. Danielli, J. M. Danielli, and J. R. Marrack, *Brit. J. Exp. Path.*, 1938, **19**, 393; M. E. Shaffer and J. H. Dingle, *Proc. Soc. Exp. Biol. Med.*, 1938, **38**, 528; A. Rothan and K. Landsteiner, *Science*, 1939, **40**, 65; E. F. Porter and A. M. Pappenheimer (jun.), *J. Exp. Med.*, 1939, **69**, 755.

Anterior Pituitary.

Gonadotrophic Hormones.—Several workers have recently succeeded in separating distinct follicle-stimulating (FSH) and luteinising fractions (LH) from pituitary extracts, using the relative insolubility of the luteinising hormone in ammonium sulphate solution at p_H 4·2 or 5—6.[1] These results were confirmed by biological assays.[2] The LH is apparently identical with the hormone of Evans, stimulating the interstitial cells of the testes and ovaries (ICSH).[3]

The follicle-stimulating hormone (FSH) contained in unfractioned pituitary extracts is a protein complex whose activity is, according to several laboratories (with the exception of A. A. Abramowitz and F. L. Hisaw[4]), relatively unaffected by digestion with commercial or crystalline trypsin, while the luteinising potency (LH) is destroyed.[5] FSH was found to be very rich in carbohydrate (principally glucosamine) when compared with the ICSH (or LH).[6] From acetylation by keten of these sugar-rich proteins, C. H. Li, M. E. Simpson, and H. M. Evans conclude that the activity of the FSH and LH is dependent on the free amino-groups.[7] H. Fraenkel-Conrat *et al.*, contrary to recent results of F. Bischoff,[8] found that cysteine destroys all gonadotrophic activity of pituitary hormones, acting upon the supposed S–S linkings considered to be essential for their potency. The chorionic gonadotrophic hormone (CGH, prolan from human pregnancy urine), however, showed no loss of activity.[9] For these and other reasons, CGH is regarded as different from pituitary luteinising hormone, with which it has some biological effects in common. CGH (of placental origin) resembles insulin in that the phenolic hydroxyls rather than the free amino-groups are essential for its activity.[7] CGH is apparently a gluco-

[1] H. L. Fevold, *Endocrinology*, 1939, **24**, 435; H. Jensen, M. E. Simpson, S. Tolksdorf, and H. M. Evans, *ibid.*, 1939, **25**, 57; H. Jensen, S. Tolksdorf, and F. Bamman, *J. Biol. Chem.*, 1940, **135**, 791; R. O. Greep, H. B. Van Dyke, and B. F. Chow, *ibid.*, 1940, **133**, 289; H. Rinderknecht and P. C. Williams, *J. Endocrinol.*, 1939, **1**, 117.

[2] H. M. Evans, M. E. Simpson, S. Tolksdorf, and H. Jensen, *Endocrinology*, 1939, **25**, 529.

[3] H. L. Fevold, *J. Biol. Chem.*, 1939, **128**, 83.

[4] *Endocrinology*, 1939, **25**, 529.

[5] W. H. McShan and R. K. Meyer, *J. Biol. Chem.*, 1938, **126**, 361; G. Chen and H. B. Van Dyke, *Proc. Soc. Exp. Biol. Med.*, 1939, **42**, 454; R. C. Li, *ibid.*, 1940, **43**, 598; B. F. Chow, R. O. Greep, and H. B. Van Dyke, *J. Endocrinol.*, 1939, **1**, 440.

[6] H. M. Evans, H. Fraenkel-Conrat, M. E. Simpson, and C. H. Li, *Science*, 1939, **89**, 249; W. H. McShan and R. K. Meyer, *J. Biol. Chem.*, 1940, **135**, 473.

[7] *J. Biol. Chem.*, 1939, **131**, 259.   [8] *Ibid.*, 1940, **134**, 641.

[9] H. Fraenkel-Conrat, M. E. Simpson, and H. M. Evans, *ibid.*, 1939, **130**, 243; *Science*, 1940, **91**, 363.

protein (4 RU per 1 μg.), the carbohydrate of which consists of hexosamine-digalactose units. The amino-group of the hexosamine is probably acetylated, and another acetyl group is attached to another part of the molecule. The minimal molecular weight lies between 60,000 and 80,000. The isoelectric point was found to be at p_H 3·2—3·3.[10]

The isolation of the interstitial cell stimulating (or luteinising) hormone in pure form (1 unit in 5 μg.) has recently been claimed by two laboratories.[11, 12]   Although the isolated proteins have similar biological properties, the results from the electrophoretic study are quite different. The isoelectric point is stated to be at p_H 7·45 and 4·6, respectively, and the mobility of the protein $6\cdot36 \times 10^{-5}$ and $0\cdot66 \times 10^{-5}$, respectively. The gonadotrophic protein of C. H. Li *et al.* contained 4·45% of mannose, 5·86% of glucosamine, and 14·2% of nitrogen with approximately 4·5% of tyrosine and 1% of tryptophan.

Thyreotrophic Hormone.—Various methods for the evaluation of the thyreotrophic potency of pituitary extracts have been proposed, of which Q. K. Smelser's test based on the increase of the thyroid weight of the one-day-old chicks may be mentioned.[13] Recent reports of the isolation of nearly pure thyreotrophic hormone with a negligible luteinising potency [14] do not support the claim that the thyreotrophic is a property of the luteinising hormone rather than due to a separate entity.[15]   J. Fraenkel-Conrat *et al.* found that this active protein contains 13% of nitrogen, 3·5% of carbohydrate, and 2·5% of glucosamine. Cysteine and keten treatment inactivates the hormone. Some metabolic effects of pituitary extracts, however, cannot be ascribed to the thyreotrophic hormone and seem to be independent of the thyroid.[16]

[10] S. Gurin, C. Bachman, and D. W. Wilson, *J. Biol. Chem.*, 1939, **128**, proc. xxxvii, 525; 1940, **133**, 467, 477; *J. Amer. Chem. Soc.*, 1939, **61**, 2251.

[11] T. Shedlovsky, A. Rothen, R. O. Greep, H. B. Van Dyke, and B. F. Chow, *Science*, 1940, **92**, 178.

[12] C. H. Li, M. E. Simpson, and H. M. Evans, *ibid.*, p. 355.

[13] Q. K. Smelser, *Proc. Soc. Exp. Biol. Med.*, 1937, **38**, 388; *Endocrinology*, 1938, **23**, 429.

[14] C. G. Lamble and V. M. Trikojus, *Biochem. J.*, 1937, **31**, 843; B. F. Chow, R. O. Greep, and H. B. Van Dyke, *J. Endocrinol.*, 1939, **1**, 440; H. L. Fevold, M. Lee, F. L. Hisaw, and E. J. Cohn, *Endocrinology*, 1940, **26**, 999; R. W. Bonsnes and A. White, *ibid.*, p. 990; J. Fraenkel-Conrat, H. Fraenkel-Conrat, M. E. Simpson, and H. M. Evans, *J. Biol. Chem.*, 1940, **135**, 235, 199.

[15] H. Jensen and J. F. Grattan, *Amer. J. Physiol.*, 1937, **37**, 388; H. Jensen and S. Tolksdorf, *Endocrinology*, 1939, **25**, 429; *Proc. Soc. Exp. Biol. Med.*, 1939, **42**, 466.

[16] D. K. O'Donovan and J. B. Collip, *Canadian Med. Assoc. J.*, 1938, **39**, 83; H. H. Neufeld and J. B. Collip, *ibid.*, p. 83; O. F. Denstedt and J. B. Collip, *ibid.*, p. 84.

Growth Hormone.—The growth of " plateaued " or hypophysectomised animals has been used for assays of the growth potency of pituitary extracts.[17] Recently J. Freud and L. H. Levie found that the growth of the tail and development of caudal vertebræ of hypophysectomised young rats ceased altogether. They use this effect upon the proliferating zone of the cartilage for assays by making *X*-ray pictures and histological examination of the tails.[18] However, thymus extracts also give a positive result in this test.[19] The evidence that there is a pituitary hormone specifically concerned with growth is convincing. Preparations of the growth hormone can be almost freed from thyreotrophic (another growth-promoting factor) and lactogenic hormone by treatment with cysteine.[20] Highly purified preparations were obtained (active in doses of 3—10 μg.) having the elementary composition : C, 49·76 ; H, 7·24 ; N, 14·27 ; S, 1·47% (in dithio-groups). They were labile in heat, acid, and alkali, and were destroyed by trypsin and pepsin. An absorption maximum was observed at 2830 A.[21]

Lactogenic Hormone.—An extensive review of this hormone has appeared.[22] All evidence indicates that the factor which initiates lactation in mammals is identical with the pigeon crop stimulating factor. Upon this fact are based most methods of assay.[23] Several workers have attempted a separation of prolactin.[24] The crystalline product of protein nature, the lowest effective dose of which was found to be 0·1—0·2 μg. per pigeon, contained C, 51·11 ; H, 6·76 ; N, 14·38 ; S, 1·77% ; tryptophan, tyrosine, and phenylalanine were identified in the preparation.[25] The isoelectric point was at p_H 5·7 and its mobility $d\mu/dp_H$ 4·5 $\times$ 10^{-5} in electrophoretic study.[26]

[17] H. M. Evans, N. Uyei, Q. R. Bartz, and M. E. Simpson, *Endocrinology*, 1938, **22**, 483.

[18] L. H. Levie, *Acta brev. neerl. Physiol.*, 1937, **7**, 119 ; J. Freud and L. H. Levie, *Arch. int. Pharmacodyn.*, 1938, **59**, 232 ; J. Freud, L. H. Levie, and D. B. Kroon, *J. Endocrinol.*, 1939, **1**, 56.

[19] L. H. Levie, I. E. Uyldert, and E. Dingemannse, *Acta brev. neerl. Physiol.*, 1939, **9**, 50.

[20] H. M. Evans, M. E. Simpson, and R. I. Pencharz, *Endocrinology*, 1939, **25**, 175 ; D. L. Meamber, H. L. Fraenkel-Conrat, M. E. Simpson, and H. M. Evans, *Science*, 1939, **90**, 19 ; A. E. Light, E. J. de Beer, and C. A. Cook, *Proc. Soc. Exp. Biol. Med.*, 1940, **44**, 189.

[21] E. Dingemanse, *Proc.* XVI *Intern. Physiol. Congr., Zürich*, 1938.

[22] S. J. Folley, *Biol. Rev.*, 1940, **15**, 421.

[23] A. J. Bergmann, J. Meites, and C. W. Turner, *Endocrinology*, 1940, **26**, 716.

[24] R. W. Bates and O. Riddle, *J. Pharm. Exp. Ther.*, 1935, **55**, 365 ; *J. Biol. Chem.*, 1938, **123**, proc. v ; A. White, H. R. Catchpole, and C. N. H. Long, *Science*, 1937, **86**, 82 ; W. R. Lyons, *Proc. Soc. Exp. Biol. Med.*, 1937, **35**, 645.

[25] A. White and G. I. Levin, *J. Biol. Chem.*, 1940, **132**, 717.

[26] C. H. Li, W. R. Lyons, and H. M. Evans, *Science*, 1939, **90**, 622 ; *J. Gen. Physiol.*, 1940, **23**, 433.

The crop-stimulating activity of prolactin depends upon the presence of free amino-groups in the molecule, as shown by its inactivation with nitrous acid,[27] with phenyl *isocyanate*,[28] and keten,[29] and depends upon the integrity of the tyrosine component, as indicated by its inactivation by iodine.[30]

Anterior Pituitary Hormones and Carbohydrate Metabolism.—The information regarding this very complicated question is at present somewhat confused and contradictory; it is nevertheless evident that pituitary extracts exert a profound influence upon metabolic processes in general (respiratory-quotient reducing substances [31]) and carbohydrate metabolism in particular. It is not certain, however, to what extent these effects can be attributed to specific hormones rather than to already known active principles.

Hypophysectomised animals tend to pass into hypoglycæmia. The glycotropic (glycostatic) pituitary principle, which counteracts this tendency, is claimed to be identical with the adrenocorticotrophic principle.[32] Certain pituitary extracts, named "diabetogenic," produce hyperglycæmia, sometimes ketonemia, and even permanent diabetes in dogs.[33] F. G. Young states that only globulin and ψ-globulin fractions have diabetogenic activity.[34]

Antihormones.—The appearance in the blood of principles antagonistic to certain hormones after pretreatment with the respective hormones seems to be established [35] beyond doubt. Whether these substances are hormones or antibodies cannot be answered with certainty as yet.　　　　　　　　　　　　　　　　E. K.

5. PROTEINS.

The great progress made during the last decade in our knowledge of proteins is mainly due to the application of physical methods and

[27] C. H. Li, W. R. Lyons, M. E. Simpson, and H. M. Evans, *Science*, 1939, **90**, 376.
[28] A. C. Bottomley and S. J. Folley, *Nature*, 1940, **145**, 304.
[29] C. H. Li, M. E. Simpson, and H. M. Evans, *Science*, 1939, **90**, 140.
[30] C. H. Li, W. R. Lyons, M. E. Simpson, and H. M. Evans, *ibid.*, 1940, **91**, 530.
[31] H. M. Evans, J. M. Luck, R. J. Pencharz, and H. C. Stoner, *Amer. J. Physiol.*, 1938, **122**, 533; J. D. Greaves, J. K. Freiberg, and H. E. Johns, *J. Biol. Chem.*, 1940, **133**, 243; W. W. Billingsley, D. K. O'Donovan, and J. B. Collip, *Endocrinology*, 1939, **24**, 63.
[32] J. F. Grattan and H. Jensen, *J. Biol. Chem.*, 1940, **135**, 511; *Amer. J. Physiol.*, 1940, **128**, 270.
[33] J. Campbell, H. C. Keenan, and C. H. Best, *Amer. J. Physiol.*, 1939, **126**, 455; F. G. Young, *Brit. Med. J.*, 1939, **2**, 393; C. H. Best, J. Campbell, and R. E. Haist, *J. Physiol.*, 1939, **97**, 200.
[34] *J. Endocrinol.*, 1939, **1**, 339.
[35] J. B. Collip, H. Seyle, and D. L. Thomson, *Biol. Rev.*, 1940, **15**, 1.

it is deemed desirable to review recent advances with a special emphasis on physicochemical work.

Molecular Size and Homogeneity.

Mainly as a result of the work of the Svedberg school, which has been reviewed in an earlier report,[1] we know that most of the proteins exist in solution as molecules of a well-defined size and that most of the usual protein preparations contain only one or few molecular species. The earlier chemical methods which claimed to isolate definite chemical individuals by making use of differences in solubility of proteins in salt solutions have thus been justified to a large extent. During the last few years, however, it has become increasingly clearer that the fact that a single sharp boundary is obtained in the ultra-centrifuge is not infallible evidence for the homogeneity of the preparation.[2] A sharp boundary, especially if it has been observed by the refractive index method, certainly shows that all the protein molecules in the solution have similar molecular weights, provided that the shapes of the molecules are also similar and are not too asymmetrical. But the fact that the molecular weights of most proteins tend to assume values which are multiples of 17,600 produces a certain *a priori* probability that a mixture of proteins will contain molecules of very similar size and thus give a fortuitous appearance of homogeneity. In fact, several such examples can be quoted. Crystalline egg albumin, which had been found to be homogeneous by sedimentation methods, has now been shown by the use of the cataphoresis method to contain two components.[3, 4] But even electrophoretic measurements, which, when performed at different acidities, furnish one of the most reliable criteria of purity, may fail to show inhomogeneities detectable by other means. Thus R. A. Kekwick[5] was able to separate serum albumin by fractional crystallisation into two crystalline and apparently homogeneous fractions, named A and B. The two fractions had the same electrophoretic mobilities between p_H 4·0 and 5·5 and identical diffusion and sedimentation constants. Fraction A contained 1·95% of carbohydrate, whereas B was almost carbohydrate-free. Similarly, several egg albumins obtained from different species of birds, which can be easily distinguished by serological reactions, show very close resemblance in electrophoresis

[1] *Ann. Reports*, 1937, **34**, 302.

[2] N. W. Pirie, *Biol. Rev.*, 1940, **15**, 377.

[3] A. Tiselius and I. B. Eriksson-Quensel, *Biochem. J.*, 1939, **33**, 1752.

[4] L. G. Longsworth, R. K. Cannan, and D. A. MacInnes, *J. Amer. Chem. Soc.*, 1940, **62**, 2580.

[5] *Biochem. J.*, 1938, **32**, 552.

experiments.[6]   It has also to be appreciated that crystallisation, which is still one of the most important methods in the purification of proteins, is not a reliable indication of purity and as a criterion of homogeneity is definitely inferior to other physical or biological methods.[2]

Another point of importance has emerged clearly from recent work on sedimentation and electrophoresis of proteins. Although for many proteins molecular size is independent of changes in the composition of the solution within rather wide limits, for other proteins this is not the case. Svedberg had already observed in his earlier work that hæmocyanin dissociates reversibly into smaller components if the p_H of the solution is outside the "stability range." But it has now been shown that a salt concentration of a molarity of 0·5—1·0 causes horse CO-hæmoglobin to dissociate into smaller molecules.[7] Similar effects are obtained on dilution. Bivalent ions seem to have a marked effect on molecular size even in small concentrations. Thus, the sedimentation constant of caseinogen showed an increase from 6×10^{-13} to 10×10^{-13} on addition of increasing amounts of calcium.[8] One of the globulin components of serum, β-globulin, is particularly sensitive to changes in salt concentration.[9] Other low-molecular substances such as urea, lysine, and ammonium chloride cause dissociation of some proteins and not of others. There is also a large amount of evidence of an interaction between different proteins. It was shown by A. S. McFarlane [10] that the sedimentation diagram of a mixture of serum albumin and globulin is not an additive pattern of the isolated proteins. Pedersen [9] has studied such interactions in a large number of cases and found that the effect varied with different proteins, and he considered that the protein-bound carbohydrate may play a part in these reactions. Electrophoretic experiments,[4] too, indicate a protein–protein interaction in the case of egg-white.

Serum Proteins.—These changes produced in the size and shape of proteins by variations in their molecular environment assume particular importance in connection with the question, how far proteins isolated from cells and biological fluids correspond to definite chemical entities in their natural state. Serum, one of the best-studied protein systems, is a case in point. The sedimentation diagram of native untreated horse serum shows in the ultra-centri-

[6] K. Landsteiner, L. G. Longsworth, and J. van der Scheer, *Science*, 1938, **88**, 83.

[7] "The Ultracentrifuge," by The Svedberg and K. O. Pedersen, Oxford, 1940.

[8] F. J. Philpot and J. St. L. Philpot, *Proc. Roy. Soc.*, 1939, *B*, **127**, 21.

[9] M. Jersild and K. O. Pedersen, *Acta path. microbiol. Scand.*, 1938, **15**, 426.

fuge two main peaks.[10]   A lighter fraction, named " albumin," represents nearly 80% and the heavier " globulin " about 20% of the total protein.   Chemical separation by half sauration with ammonium sulphate gives a ratio of albumin to globulin of nearly 1, and the same ratio is approached from the sedimentation diagram if the serum is suitably diluted.   Thus the " albumin " peak can be resolved into two components, of which one is due to albumin proper and the other one to a protein called X by McFarlane and later shown by Pedersen [7, 9] to be identical with a globulin, named β-globulin by A. Tiselius.   The variability of the sedimentation of this protein is caused by its extreme sensitivity to changes in the salt concentration of the medium.   More important information concerning the complex system of proteins in serum and plasma was, however, obtained by the elegant electrophoretic method of Tiselius. It was shown that serum contains four components which could be distinguished by their different mobilities in an electrical field ; in addition to serum albumin there are three different globulins, labelled α, β, and γ,[11] having different mobilities but nearly identical molecular weights.   More recently I. A. Luetscher [12] has demonstrated in human serum two albumin peaks at p_H 4·0, and a similar observation was made for mouse serum.[13]   By improved optical methods it was shown that the β-component of human serum is actually composed of two substances, labelled β_1 and β_2.[14, 15]

The values for the relative amounts of the various components in normal human serum given by different workers vary slightly, the average value for albumin being about 65%, which gives an albumin-globulin ratio of 2 : 1 ; the α-globulin is present in only small amounts.   Plasma, as might be expected, contains another electrophoretically well-defined protein, fibrinogen.[16]

It is extremely difficult to correlate these electrochemical investigations, which study the protein complex of serum in its native state, with the results of workers who isolate proteins by chemical methods, such as salting-out or fractional crystallisation.   It is certain that the classification of serum proteins on the basis of these old methods cannot now be accepted.   It has been shown, e.g., that " pseudo-globulin" and " euglobulin " are mixtures and that " albumin " as usually prepared contains in fact a large proportion of globulin.[17]

[10] *Biochem. J.*, 1935, **29**, 407.

[11] A. Tiselius, *ibid.*, 1937, **31**, 313, 1464; R. A. Kekwick, *ibid.*, 1939, **33**, 1122.

[12] *J. Clinical Invest.*, 1940, **19**, 313.

[13] J. Bourdillon and E. H. Lennette, *J. Exp. Med.*, 1940, **72**, 11.

[14] H. I. Svensson, *Kolloid-Z.*, 1939, **87**, 181.

[15] R. A. Kekwick, *Biochem. J.*, 1940, **34**, 1248.

[16] E. Stenhagen, *ibid.*, 1938, **32**, 719.

[17] L. F. Hewitt, *ibid.*, 1936, **30**, 2229; 1938, **32**, 26.

This does not mean that fractionation by chemical methods is useless; on the contrary, the Reporter believes that important results by such methods can still be obtained if the separation is followed by physical methods, especially by electrophoretic measurements. A very good example for such a controlled separation is Kekwick's isolation of β-globulin by fractional precipitation with sodium sulphate.[15]

These requirements are not fulfilled in many recent papers dealing with serum proteins; it seems desirable, however, to review the rather complicated position at the present juncture. It was the merit of L. F. Hewitt [17] to reopen the problem of the homogeneity of serum albumin and he was able to isolate three main fractions : (1) a crystalline fraction, named crystalbumin, with practically no carbohydrate, $[\alpha_D] - 71°$, high tyrosine and cystine content, and a content of tryptophan of 0.26%; (2) an amorphous, carbohydrate-rich fraction, seroglycoid, with $[\alpha_D] - 57°$, low cystine content and a tryptophan content of 1%; (3) a fraction, globoglycoid, behaving like a globulin after crystalbumin has been removed and containing carbohydrate. Hewitt's findings have recently been criticised by C. Rimington,[18] who has also prepared a protein very rich in carbohydrate from ox-serum and named it seromucoid. There is general agreement that a crystalline fraction can be prepared from crude albumin which is carbohydrate-free; this fraction is probably identical with Kekwick's serum albumin B.[5] But even this preparation is not homogeneous, as two boundaries of p_H 4·0 were demonstrated by electrophoretic experiment.[19] An apparently homogeneous fraction was, however, obtained by crystallising the albumin sulphate at p_H 4·0 from water.[20]

The albumin fraction contains proteins with a high content of carbohydrate which have not been examined by physical methods; it seems very likely that the preparations called " seromucoid " by Rimington and " seroglycoid " by Hewitt are very similar and differ only in their respective " impurities." Whether Kekwick's crystalline serum albumin A is a chemical individual or a complex formed between crystalbumin and seromucoid remains doubtful. It seems established that the albumin fraction contains an appreciable quantity of globulin-like material; but whether a new name should be coined for this rather ill-defined preparation is less certain. From a broader point of view the most important question in this connection is, whether serum contains a small number of distinct proteins which are in every respect chemical individuals and in which the

    [18] *Biochem. J.*, 1940, **34**, 931; C. Rimington and M. van den Ende, *ibid.*, p. 941.
    [19] J. A. Luetscher, *J. Amer. Chem. Soc.*, 1939, **61**, 2888.
    [20] T. L. McMeekin, *ibid.*, p. 2884.

difficulties of isolation are due to a lack of specificity of the analytical methods used and the interaction of proteins with each other discussed above; or whether the proteins of serum contain an indefinite number of molecular species which fall into groups of certain physical and chemical similarity—a fact which would be responsible for an apparent and deceptive uniformity in physical and biological behaviour of different fractions. Physical experiments, such as electrophoresis, seem to favour the first, non-defeatist theory.

Changes in Serum Proteins in Disease.

The examination of pathological sera by modern physical methods is a very promising field, opened by A. S. McFarlane,[21] using ultra-centrifugal methods. More recently the cataphoresis technique has been applied and some interesting results have been obtained. The most striking changes occur in multiple myelomatosis, which had been known for some time to be associated with a hyperproteinemia and a change in the albumin–globulin ratio. From the results of different workers (Kekwick; [15] Jersild and Pedersen; [9] L. G. Longsworth, Th. Shedlovsky, and D. A. MacInnes [22]) it appears that in all cases the relative proportion of globulin is very much increased. In one group of cases this is due to an increase in the γ-globulin peak; in others an excess of β-globulin was apparent. Nephrosis leads also to a change in β-globulin which is associated with the presence of a protein–lipoid complex; this combination is apparently broken down by ether extraction.[23] Febrile patients, on the other hand, show an increase in α-globulin.[22]

Shape of Protein Molecules.

Whereas the size of proteins can be determined by methods which rest on a secure thermodynamic basis such as sedimentation equilibrium measurements, exact information as to the shape of the molecules is more difficult to obtain. Broadly speaking, proteins other than fibrous proteins can be divided into two classes. The first group comprises highly asymmetrical types such as myosin and many virus nucleoproteins which show double refraction of flow at comparatively small velocity gradients and " anomalous viscosity "; i.e., the viscosity of their solutions depends markedly on the rate of flow. The second group is made up of the so-called " globular " proteins, which do not show any definite orientation if the usual rates of flow are applied. These molecules are either spherical or do not deviate much from a symmetrical shape.

The methods most extensively used to estimate the degree of

[21] *Biochem. J.*, 1935, **29**, 1175.   [22] *J. Exp. Med.*, 1939, **70**, 399.
[23] L. G. Longsworth and D. A. MacInnes, *ibid.*, 1940, **71**, 77.

asymmetry of " globular " proteins are based either on a comparison between observed and calculated diffusion or frictional constants or on viscosity measurements. The " observed " frictional constant, f, can be calculated from the diffusion constant or from the molecular weight, M, partial specific volume and sedimentation constant; the two methods give generally identical results. On the other hand, a " theoretical " frictional constant, f_0, can be calculated if it is assumed that the particle of the molecular weight M is rigid, spherical and does not combine with the solvent. In most cases f and f_0 are not identical and the ratio f/f_0, which is called the frictional ratio, is greater than 1. This indicates that the particles either are solvated or are not spherical. Attempts have been made to assess the dimensions of protein molecules in solution by assuming that hydration can be neglected and that the shapes of the particles are those of ellipsoids of rotation.[24] These assumptions are, however, to a large extent arbitrary. Hydration cannot be neglected and may account in many cases for the values of the frictional ratio. Thus G. S. Adair [25] has shown that the observed diffusion constants of egg albumin, hæmoglobin, and serum albumin can be quantitatively explained in terms of spherical shapes, if it is assumed that these molecules have a symmetrical shell of hydrated solvent equal in amount to that found for their crystals. It will be difficult to correct for hydration in all cases; our knowledge of the forces operating in hydration and their magnitude is still incomplete and different methods have yielded different results. Moreover, it is quite possible that, if hydration is largely due to electrostatic interaction of charged groups of the protein surface with the dipolar solvent molecules, asymmetrical hydration will take place with symmetrical particles provided that the charge density is asymmetrical. In that case the increase of the frictional ratio will be greater than could be accounted for by mere increase in volume. But, even if solvation could be neglected, the use of an ellipsoidal model is somewhat arbitrary; any marked irregularity of the molecular surface will cause an increase in f.

It is generally accepted that there exists a close relationship between the shape of molecules and the viscosity of their solutions, although the quantitative significance of the different calculations is less certain. W. Kuhn [26] has given an equation correlating the observed specific viscosities of solutions containing molecules of the shape of long cylinders with their axial ratios and J. M. Burgers [27]

[24] H. Neurath, *J. Amer. Chem. Soc.*, 1939, **61**, 1841.
[25] *Proc. Roy. Soc.*, 1939, *B*, **127**, 18.
[26] *Z. physikal. Chem.*, 1932, *A*, **161**, 1.
[27] Second report on viscosity and plasticity, Amsterdam, 1938.

made similar calculations for elongated ellipsoids; A. Polson [28] proposed a semi-empirical formula which has given quite satisfactory results. The last equation can be considered to be a modification of Kuhn's formula, including, however, a correction for hydration. In all these calculations it is assumed that the Brownian movement is sufficient to suppress any orientation of the particles due to the hydrodynamic force applied. This assumption is almost certainly justified if the specific viscosity is independent of the rate of shear, that is, for most " globular " proteins. As pointed out by J. R. Robinson,[29] the position becomes more complicated in the case of highly asymmetrical particles, like tobacco mosaic virus or myosin; here work has to be done to rotate the molecules and this amount of energy becomes less as the velocity gradient is increased, compared with the energy required to maintain the rate of flow. Measurements with ordinary capillary viscometers are in such cases open to grave objections. These equations have been used by several authors to deduce the shapes of globular proteins,[28, 30, 31] and the results obtained would indicate that nearly all the proteins which had hitherto been considered spherical have axial ratios of 1 : 3— 1 : 8. These figures must, however, be accepted with some reserve. The difficulties concerning the uncertainty of hydration and shape of the particles, mentioned in connection with the frictional ratios, apply equally to the interpretation of viscosity measurements. J. W. Mehl, J. L. Oncley, and R. Simha [32] have compared the values obtained from frictional ratios and from viscosity measurements and found that agreement between these methods is not satisfactory if the equations of Kuhn and Burgers are applied. An equation derived by Simha [33] gives better results. The whole problem of viscosity and shape has also recently been reviewed by J. M. Burgers,[34] who calculated theoretical sedimentation constants from the axial ratios obtained by viscosity measurements, assuming ellipsoidal shape, and compared these values with those observed in sedimentation experiments. The agreement was not very good, even if allowance was made for hydration. It is felt that, although the quantitative interpretation of results obtained by viscosity measurements is doubtful, they may yield important information. Thus the increase of the viscosity of egg albumin [31] on denaturation cannot be explained by increased hydration and must be due to an increased asymmetry of shape.

[28] *Kolloid-Z.*, 1939, **88**, 51.   [29] *Proc. Roy. Soc.*, 1939, *A*, **170**, 519.

[30] H. Neurath and G. R. Cooper, *J. Amer. Chem. Soc.*, 1940, **62**, 2248.

[31] H. B. Bull, *J. Biol. Chem.*, 1940, **133**, 39.

[32] *Science*, 1940, **92**, 132.   [33] *J. Physical Chem.*, 1940, **44**, 25.

[34] *Proc. K. Akad. Wetensch. Amsterdam*, 1940, **43**, 307.

Interesting observations have also been recently reported on anomalous viscosities of proteins obtained from developing eggs and embryos.[35] The results, which were obtained by the use of a Couette viscometer, indicate that these proteins are highly asymmetrical.

The most reliable criterion of a marked asymmetry of shape is double refraction of flow. By the use of this method it was shown that myosin molecules are long and rod-shaped particles,[36] an interpretation which is in accordance with all other physical properties of this protein. Later it was shown by several workers that many other proteins show double refraction of flow at low velocity gradients. Thus a highly asymmetrical shape was proved for tobacco mosaic virus,[37] other plant viruses,[38, 41] fibrinogen,[39] antibody globulins,[40] hog thyreoglobulin, different hæmocyanins,[41] and ovoglobulin.[42] The quantitative aspects of the relationship between double refraction of flow and the dimensions of particles have recently been discussed by J. W. Mehl,[43] who, using the theoretical treatment of P. Boeder[44] and W. Kuhn,[26] calculated the length of the myosin molecule to be about 8500 A. Such calculations are based on certain simplifications, as Mehl himself points out, and the calculated dimensions cannot be considered extremely accurate.

The influence of different chemical and physical factors on the shapes of these highly asymmetrical particles has recently been investigated. It was found, *e.g.*, that the double refraction of flow of myosin is abolished by such substances as the chlorides of bivalent cations, guanidinium salts, and potassium iodide in very dilute solution,[45] and urea produced a similar effect in more concentrated solution. The loss of double refraction of flow was associated with a decrease of viscosity, indicating that " denaturation " in this case consisted in a definite decrease of the asymmetry of the molecule; as mentioned above, globular proteins show the opposite behaviour.

The recently developed electron microscope has also been used to

[35] A. S. C. Lawrence, J. Needham, and Shih-Chang Shen, *Nature*, 1940, **146**, 104.

[36] A. L. von Muralt and J. T. Edsall, *J. Biol. Chem.*, 1930, **89**, 315, 351.

[37] F. C. Bawden, N. W. Pirie, J. D. Bernal, and I. Fankuchen, *Nature*, 1936, **138**, 1951; M. A. Lauffer, *J. Physical Chem.*, 1938, **42**, 935.

[38] G. A. Kausche, H. Guggisberg, and A. Wissler, *Naturw.*, 1939, **27**, 303; H. S. Loring, *J. Biol. Chem.*, 1938, **126**, 455.

[39] G. Boehm and R. Signer, *Klin. Woch.*, 1932, **11**, 599.

[40] E. A. Kabat, *J. Exp. Med.*, 1939, **69**, 103.

[41] M. A. Lauffer and W. M. Stanley, *J. Biol. Chem.*, 1938, **123**, 507.

[42] G. Boehm and R. Signer, *Helv. Chim. Acta*, 1931, **14**, 1370.

[43] *Cold Spring Harbor Symposia Quantitat. Biol.*, 1938, **6**, 218.

[44] *Z. Physik*, 1932, **75**, 258.

[45] J. T. Edsall and J. W. Mehl, *J. Biol. Chem.*, 1940, **133**, 409.

observe directly the shapes of colloidal particles. Thus M. von Ardenne [46] has recently published photographs of spherical *Helix* hæmocyanin molecules and two different viruses which appear in the form of long threads.   Photographs of tobacco mosaic virus particles obtained by an electron diffraction method have also been published by G. A. Kausche, E. Pfankuch, and H. Ruska,[47] who state that these particles are about 150 A. in cross-section and about 3000 A. in length.   The dimensions obtained were of the same order of magnitude as those obtained by other methods, such as viscosity.   The electron microscope has also been used to study the reaction between colloidal gold particles and tobacco mosaic virus.[48]   These photographs were obtained on dried films, and the shapes and sizes observed are therefore not necessarily those of native proteins or viruses.   A. N.

6. Physicochemical Phenomena.

Metalloporphyrins.

W. M. Clark and his colleagues [1] have made an extensive survey of the use of oxidation–reduction potentials and spectrophotometry in the analysis of the behaviour of metalloporphyrins in the presence of substances capable of co-ordinating with the metal atom. Equations are obtained relating electrode potential, total concentration of metalloporphyrin, total concentration of base co-ordinating with the metal atom, the ratio of the concentrations of the oxidised and the reduced complex, the number of electrochemical equivalents involved in the oxidation–reduction process, constants describing the dissociation of the base metalloporphyrin complexes (both the reduced complex and the oxidised complex), the numbers of molecules of base co-ordinating with the metal atom (a) when reduced, (b) when oxidised, and the degree of association of the oxidised and the reduced metalloporphyrin molecules.   Equations are also given by which the various equilibrium constants may be derived from spectrophotometric data.   Sixteen propositions are given which are open to experimental investigation, and graphical methods are outlined for determining dissociation constants, etc., from potential measurements.   Thus the analysis of these results is placed on an objective basis.   This work has not so far led to many fundamentally

[46] *Naturwiss.*, 1940, **28**, 113.

[47] *Ibid.*, 1939. **27**, 292.

[48] G. A. Kausche and H. Ruska, *Kolloid-Z.*, 1939, **89**, 21.

[1] W. M. Clark, J. F. Taylor, T. H. Davies, and C. S. Vestling, *J. Biol. Chem.*, 1940, **135**, 543; J. F. Taylor, *ibid.*, p. 569; T. H. Davies, *ibid.*, p. 597; C. S. Vestling, *ibid.*, p. 623; W. M. Clark and M. E. Perkins, *ibid.*, p. 643.

new conclusions, but it makes possible the drawing of objective conclusions on many hitherto controversial points.

Protein Adsorption and the Suspended Fat of the Blood.

A. C. Frazer and his colleagues have investigated the factors responsible for the stability of the suspended plasma neutral fat. According to Frazer [2] the fat is mainly contained in the chylomicrons, which are microscopic or submicroscopic fatty droplets protected by an adsorbed layer of protein. Towards precipitants such as ammonium sulphate, chylomicrons behave like globulins, but when centrifuged the chylomicrons move in the centripetal direction, unlike the serum globulins. Similar behaviour is shown by artificial fat emulsions in the presence of globulins. Albumins also protect the artificial emulsions, but the precipitation reaction differs from that of chylomicrons and fat globules in the presence of globulin. Frazer concludes that the chylomicrons consist mainly of neutral fat, but that the outer layer which controls the precipitation reactions is adsorbed globulin. A. Tiselius [3] has shown that the opalescence of normal serum, which is probably due to fat droplets, migrates on electrophoresis as though the particles were coated with β-globulin, and L. G. Longsworth and D. A. McInnes [4] have shown that in serum from cases of lipoid nephrosis the lipoid behaves electrophoretically like β-globulin, after cold ether extraction much of it is removed from the serum, and the β-globulin peak of the electrophoretic pattern is correspondingly reduced.

Protein adsorption at oil–water interfaces has been studied by many authors,[5] with conclusions compatible with those of Frazer. The first layer of protein adsorbed is denatured, as at the air–water interface, but on this layer a second layer of globular protein may be adsorbed and this layer will control the precipitation and electrophoretic properties of the interface. The loss of toxicity of toxins and venoms after mixing with oil emulsions [6] is probably due mainly to the denaturation of proteins adsorbed on the oil droplets.

<div align="right">J. F. D.</div>

[2] J. J. Elkes, A. C. Frazer, and H. C. Stewart, *J. Physiol.*, 1939, **95**, 68; A. C. Frazer and H. C. Stewart, *ibid.*, 4 P, 5 P.

[3] *Kolloid-Z.*, 1937, **31**, 1464.   [4] *J. Exp. Med.*, 1940, **71**, 77.

[5] J. F. Danielli and E. N. Harvey, *J. Cell. Comp. Physiol.*, 1934, **5**, 483; H. Devaux, *Comp. rend.*, 1936, **202**, 1957; I. Langmuir and D. F. Waugh, *J. Gen. Physiol.*, 1938, **21**, 745; J. F. Danielli, *Cold Spring Harbor Symposia*, 1938, **6**, 190; A. E. Alexander and T. Teorell, *Trans. Faraday Soc.*, 1939, **35**, 727; F. A. Askew and J. F. Danielli, *ibid.*, 1940, **36**, 785.

[6] G. N. Myers, *J. Hyg.*, 1934, **34**, No. 2; A. C. Frazer and V. G. Walsh, *Brit. Med. J.*, 1934, March; J. Oerskov and S. Schmidt, *Rev. Immunol.*, 1935, **1**, No. 4; A. C. Frazer and V. G. Walsh, *J. Pharm. Exp. Ther.*, 1939, **67**, 470.

7. Biological Catalysis.

As befits the fundamental object of biochemical research, enzymic processes continue to be studied with ever-increasing revelation of their mechanisms. In particular, studies of oxidation, of C–C link disruption, and of reversible phosphorolytic breakdown of starch have yielded important results.

Oxidation Mechanisms.*

A number of reconstructed biological oxidations can take place through three essentially similar stages, viz. :

(a) $\underbrace{\text{Substrate} + \text{coenzyme I(or II)}}_{\textit{Specific dehydrogenase}} \longrightarrow$

oxidised substrate + dihydrocoenzyme I(or II)

(b) $\underbrace{\text{Dihydrocoenzyme I(or II)} + 2Fe^{III} \text{ cytochrome}}_{\textit{Dihydrocoenzyme I(or II)-dehydrogenase}} \longrightarrow$

coenzyme I(or II) + $2Fe^{II}$ cytochrome

(c) $\underbrace{2Fe^{II} \text{ cytochrome} + \frac{1}{2}O_2}_{\textit{Cytochrome oxidase}} \longrightarrow 2Fe^{III}$ cytochrome + H_2O
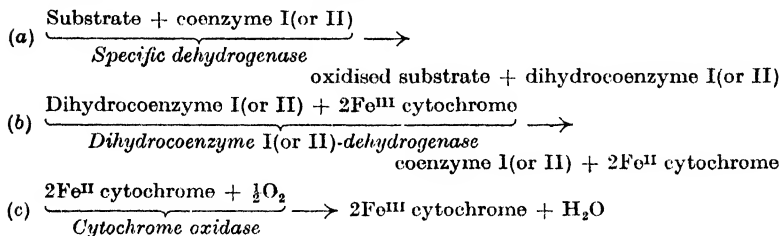
(a), (b), and (c) each consist in the transfer of two hydrogen atoms (or their equivalent) from a hydrogen donator to a hydrogen acceptor under the influence of an enzyme highly specific with respect both to donator and to acceptor. Modern nomenclature tends to reserving the term " oxidase " for enzymes directly catalysing the reduction of molecular oxygen. Reactions (a) and (b) are anærobic, whereas (c) is ærobic. It is not yet clear whether, in vivo, the reoxidation of dihydrocoenzymes takes place through the cytochrome system or whether some alternative mechanism is concerned. It is, however, significant that it is generally believed that cyanide, known to inhibit cytochrome oxidase, blocks the greater part of most tissue-respiration.

In this brief review it is convenient to regard both enzymes and carriers as catalysts. The view has recently been put forward that coenzymes I and II (loosely termed " phosphopyridine nucleotides ") should not be regarded as individual catalysts, but as being dissociably linked to " specific proteins " (the dehydrogenases) and thus forming the prosthetic group of a catalytically-active conjugated protein. This idea has been suggested from the recognition of the nature of the cytochromes and of the so-called " flavoproteins " (Report for 1939, p. 353). M. Dixon and L. G. Zerfas,[1] however, have in-

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[1] *Biochem. J.*, 1940, **34**, 371.

* D. E. Green, "Mechanisms of Biological Oxidations" (Cambridge Univ. Press, 1940).

geniously obtained evidence in direct contradiction to this conception and in support of the older and more widely held view. By choosing appropriate substances to act as hydrogen-acceptors, they showed that both the alcohol and the maleic dehydrogenases of yeast could oxidise their appropriate substrates in complete absence of coenzyme I. They therefore regard the " protein " of the dehydrogenases as the complete enzyme and point out that coenzyme I and the " protein " are in the relation of substrate to enzyme as indicated in (a) above.

The cytochromes and the succinic dehydrogenase system have been the subject of new investigations by D. Keilin and E. F. Hartree.[2] They emphasise that attempts to dissect the system (which oxidises succinate aerobically) have failed. The activity of the system depends on the presence of insoluble particles to which the catalysts are bound. The generally accepted course of succinate oxidation may be expressed as follows :

(d) $\underbrace{\text{Succinate} + 2Fe^{III} \text{ cytochrome-}c}_{\textit{Succinic dehydrogenase}} \longrightarrow$ fumarate $+ 2Fe^{II}$ cytochrome-c

(e) $\underbrace{2Fe^{II} \text{ cytochrome-}c + \frac{1}{2}O_2}_{\textit{Cytochrome oxidase}} \longrightarrow 2Fe^{III}$ cytochrome-c + H_2O
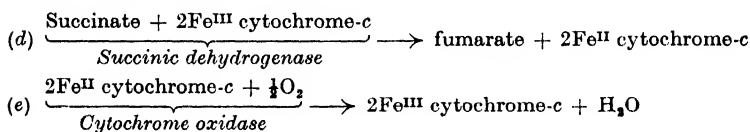
But Keilin and Hartree have found that with certain oxidase preparations reaction (d) would not proceed. They suggest that the reduction of Fe^{III} cytochrome-c may be an indirect one, requiring the intermediate intervention of cytochrome-b or some hitherto unrecognised substance. These authors have recognised, in heart-muscle, insect thoracic-muscle, baker's yeast, and strictly aerobic bacteria a new cytochrome component, termed a_3. This has many properties identifying it with the enzyme, cytochrome oxidase ; e.g., it is thermolabile and is, in the Fe^{II} state, very easily autoxidisable. Carbon monoxide combines with the Fe^{II} compound, giving a stabilised derivative, whereas the Fe^{III} form combines reversibly with potassium cyanide, hydrogen sulphide, sodium azide, etc. On the other hand, it has so far not been possible to demonstrate either direct or indirect reduction of $Fe^{III}a_3$ by $Fe^{II}c$ under strictly anaerobic conditions and in complete absence of other reducing substances. The original papers should be consulted.

Fission of the C–C Link.

Remarkably little is known of biological processes involving the degradation of a carbon chain. Carboxylase (which decarboxylates α-keto-acids, $CHR_1R_2 \cdot CO \cdot CO_2H$) and zymohexase (which splits

² *Proc. Roy. Soc.*, 1939, *B*, **127**, 167; 1940, *B*, **129**, 277.

fructofuranose 1 : 6-diphosphate into glyceraldehyde 3-phosphate and dihydroxyacetone phosphate) are probably the only authentic members of this class to be identified as individuals.

Pyruvate is known to undergo two different degradation processes *in vivo*. In yeast, carboxylase in the presence of thiamine (aneurin) diphosphate, forms acetaldehyde and carbon dioxide from pyruvate. In animal tissues, and in certain bacteria, pyruvate is oxidised to acetate and carbon dioxide, thiamine diphosphate again being necessary. D. E. Green, D. Herbert, and V. Subrahmanyan [3] describe the isolation from brewer's yeast of a highly active, stable preparation of carboxylase containing 0·46% of thiamine diphosphate and 0·13% of magnesium, no other metal being detected. The authors regard their material as containing the complete enzyme. In high concentrations of salts the three components, protein, magnesium, and thiamine diphosphate, are bound together; on dilution, dissociation takes place. Other bivalent cations can replace magnesium; the following were found active in descending order : Mn, Mg, Fe^{II}, Cu, Cd, Zn.

The oxidative fission of pyruvate by preparations of *Bact. delbrückii* has been studied by F. Lipmann.[4] The original papers should be studied for details; for present purposes it will suffice to discuss Lipmann's views on the part played by phosphate in this reaction. Recognising the importance of *enol*pyruvic acid phosphate in glycolysis (Report for 1939, p. 358), he sought for possible phosphorylated intermediaries in the oxidation. He found (i) that phosphate was transferred to adenylic acid, and (ii) that crude acetyl phosphate [5] in the presence of the bacterial material could serve as a source of phosphate for reaction (i). Lipmann has therefore suggested the following scheme for this oxidation :

Pyruvate + phosphate − 2 hydrogen ⟶ Acetyl phosphate + carbon dioxide
Acetyl phosphate + adenylic acid ⟶ Acetate + adenylpyrophosphate.

It should be noted that S. Ochoa, R. A. Peters, and L. A. Stocken [5a] report that acetyl phosphate does not act as an intermediary in pyruvate oxidation by brain nor does it act as a phosphate donor to adenylic acid in muscle extract.

The widely distributed zymohexase (Report for 1939, p. 359) has been obtained as a very active preparation by D. Herbert, H. Gordon, and V. Subrahmanyan [6] from the water-soluble protein of

[3] *J. Biol. Chem.*, 1940, **135**, 795.
[4] *Nature*, 1939, **144**, 381; *Cold Spring Harbor Symposium on Quantitative Biology*, 1939, **7**, 248; *J. Biol. Chem.*, 1940, **134**, 436.
[5] E. Kamerer and G. Carius, *Annalen*, 1864, **131**, 165.
[5a] *Nature*, 1939, **144**, 750.   [6] *Biochem. J.*, 1940, **34**, 1108.

rabbit muscle. Some 4% of this fraction was isolated with an activity 150 times greater than that of the original tissue. The preparation was non-crystalline and contained C, 50·6; H, 7·04; N, 15·8; S, 1·25%; neither phosphorus nor iodine nor significant amounts of carbohydrate were detected. An exhaustive study of the enzyme was made; it was concluded that no oxidisible or reducible group was concerned in its activity; heavy metals had a marked inhibitory effect. The material was examined by E. C. Bate Smith in the Tiselius apparatus.

The Reversible Phosphorolysis of Starch : Phosphorylation of Glucose.

In the Report for 1939 (pp. 359, 361) mention was made of the reversible splitting of glycogens from liver, muscle, and yeast into glucopyranose 1-phosphate. Two papers by C. S. Hanes [7] describe the extension of this work to starch, enzymic preparations having been obtained from both pea-seeds and potatoes (see this vol., pp. 419, 421). In such systems the normal course undergone by the glucose 1-phosphate is its conversion into hexose-6-phosphates. Only if the latter reaction can be prevented does the 1-phosphate accumulate. In that event synthesis of the polysaccharide tends to result, as the enzymic equilibrium is on the side of synthesis. It would therefore be of interest to demonstrate the production by enzymes of the 1-phosphate from glucose and $H_2PO_4^-$. This has not yet been done.

Although yeast preparations are believed to esterify carbohydrate with phosphoric acid, it is only recently that the phosphorylation of glucose by animal tissues has been demonstrated, although only with respect to kidney extracts. H. Kalckar [8] has shown that phosphoric esters accumulate in such extracts, under aerobic conditions, when fluoride is added to inhibit phosphatase activity. The process is stimulated by the presence of alanine, glutamic, citric, and fumaric acids, all of which can be oxidised by the kidney. Later, S. P. Colowick, M. S. Welch, and C. F. Cori [9] showed that fructose diphosphate and glyceric acid phosphate are formed in aerobic kidney extracts in the presence of fluoride. The authors consider that the phosphorylating activity is effected through energy derived from the oxidation processes involving dicarboxylates, *e.g.*, succinate to fumarate. Adenylic acid, coenzyme I and Mg·· are necessary. The same authors [10] have further shown that, in the absence of fluoride, added fumarate catalyses the oxidation both of glucose and of

[7] *Proc. Roy. Soc.*, 1940, *B*, **128**, 421; **129**, 174.
[8] *Enzymologia*, 1939, **6**, 209.
[9] *J. Biol. Chem.*, 1940, **133**, 359.   [10] *Ibid.*, p. 641.

pyruvate by dialysed kidney extract. They therefore consider that fumarate is an essential link between the phosphorylation of glucose and its subsequent oxidation.

Carbonic Anhydrase and Zinc.

D. Keilin and T. Mann [11] have isolated extremely active protein preparations from erythrocytes and gastric mucosa. The material is remarkable in containing zinc, which appears to be necessary for its activity. It has further been shown [12] that sulphanilamide, and in general, sulphonamides, act as specific inhibitors for carbonic anhydrase.

Crystalline Preparations of Enzymes.

The following list gives those enzymes which to date have been obtained in the form of crystalline protein preparations. (For a discussion on the problem of the homogeneity of crystalline proteins, see this vol., p. 405.)

Pepsin,[13] pepsinogen, trypsin, trypsinogen, chymotrypsin, chymotrypsinogen, papain,[14], carboxypeptidase, nuclease,[15] urease, catalase, alcohol dehydrogenase, triosephosphate dehydrogenase,[16] lactic dehydrogenase of heart,[17] tyrosinase.[18]

(References are given only to the most recent advances.)

D. J. B.

8. PLANT BIOCHEMISTRY.

Some Products and Enzymes of Plants.

Starch and Amylases.—One of the outstanding achievements of the year in the field of carbohydrate biochemistry is due to C. S. Hanes,[1] who has published interesting and valuable papers on the breakdown and synthesis of starch in the higher plants, and has been able to effect the synthesis *in vitro*. The origin of the investigations may be said to arise from an attempt to discover whether the phosphorylated sugars play a similar rôle in the carbohydrate metabolism of the higher plants, to that which they have been shown to

[11] *Biochem. J.*, 1940, **34**, 1163.

[12] T. Mann and D. Keilin, *Nature*, 1940, **146, 164**.

[13] V. Desreux and R. M. Herriot, *ibid.*, 1939, **144,** 289.

[14] A. K. Balls and H. Lineweaver, *J. Biol. Chem.*, 1939, **130,** 669.

[15] M. Kunitz, *J. Gen. Physiol.*, 1940, **24,** 15.

[16] O. Warburg and W. Christian, *Biochem. Z.*, 1939, **303,** 40.

[17] F. B. Straub, *Biochem. J.*, 1940, **34,** 483.

[18] H. R. Dalton and J. M. Nelson, *J. Amer. Chem. Soc.*, 1939, **61, 2946**.

[1] *Proc. Roy. Soc.*, 1940, *B*, **128,** 421.

do in the case of yeast and some animal tissues.   Necessary stepping stones to the proof of such a theory are the discovery of phosphorylated sugars, and of enzymes capable of acting on them, in the plant economy.   A phosphorylating enzyme had been discovered by J. Bodnar [2] in 1925 in the flour from ground mature peas, and B. Tankó [3] in 1936 was able to show that such an enzyme converted inorganic phosphate in a phosphate buffered mixture of the flour into fructofuranose 1 : 6-diphosphate.   Hexose monophosphates also were present.   Hanes has found that the enzyme, termed phosphorylase, separated from the tissue, is able to phosphorylate starch and a number of starch dextrins and that simple sugars with the exception of maltose, which is attacked only slowly, are unattacked.   The first product in the phosphorylation of starch is the non-reducing glucose 1-phosphate, and this is found to be a reversible reaction in that addition of glucose 1-phosphate to an extract of peas involves the production of a certain proportion of starch with liberation of free phosphate.   An alternative transformation of glucose 1-phosphate involving two distinct enzymic actions has been observed : the glucose 1-phosphate rapidly disappears from the system and a mixture of glucose-, fructose-, and mannose-6-phosphate is produced.   Tankó's observation that hexose diphosphate is formed when pea flour suspensions act in presence of phosphate is confirmed and it is further found that addition of starch to the mixture greatly accelerates the esterification.   If dialysed extracts are used, however, the diphosphate is not formed and it appears that such formation depends on the presence of a dialysable co-enzyme.

The glucose 1-phosphate appears to be identical with that obtained as the first product of esterification in the action of muscle phosphorylase on glycogen.[4]

Observation shows that it is probable that the glucose 1-phosphate arises by direct phosphorylation of the saccharide chains in starch. Thus starch and complex dextrins are esterified more rapidly and completely than the lower members of the starch–maltose series ; that the higher members are directly involved in the reaction is shown by the decrease in iodine colour under phosphorylase action ; and the change in iodine colour corresponds with what might be anticipated from an endwise degradation of the chains.   Glucose itself is not esterified and from these facts it is concluded that terminal glucose units of the chains are phosphorylated and liberated from non-aldehydic chain-ends.

[2] *Biochem. Z.*, 1925, **165**, 1.
[3] *Biochem. J.*, 1936, **30**, 692.
[4] C. F. Cori and G. T. Cori, *Proc. Soc. Exp. Biol. Med.*, 1936, **34**, 702.

Hanes summarises the preceding results as follows :

$$\text{Starch} \underset{- \text{ phosphate}}{\overset{\substack{\text{I } (Phosphorylase) \\ + \text{ phosphate}}}{\rightleftharpoons}} \text{Glucose 1-phosphate}$$

III
(*Phosphoglucose-conversion enzymes*)

II
(*Amylase*)

Reducing hexose 6-phosphates

IV
(*Enzyme + dialysable co-enzyme*)

+
water

+
phosphate

Dextrins, maltose, glucose

Fructose 1 : 6-diphosphate
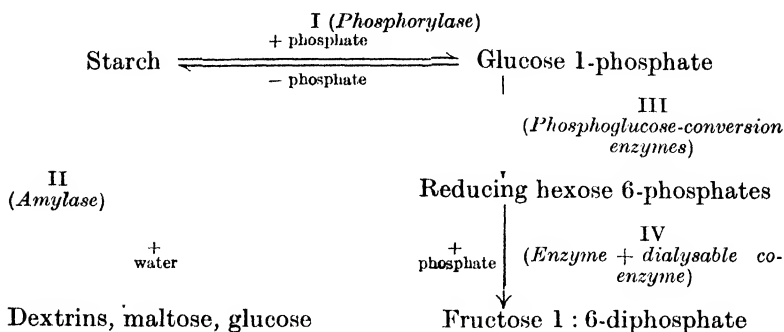
At a later stage, Hanes [5] describes the preparation of phosphorylase from potato tubers; the enzyme is obtained in highly active form and is free from those enzymes which promote the alternative transformations already referred to. The reversibility of the starch–glucose 1-phosphate reaction is shown, since the ratio of inorganic phosphate to ester reaches the same value in either direction. Moreover, the equilibrium point is not affected by wide variations in concentrations of the reactants or enzyme. The position of equilibrium is notably altered by changes in p_H and it has been shown that this is due to the effect of varying hydrogen-ion concentration on the dissociation of inorganic and ester phosphate. The bivalent ions determine the equilibrium, and between p_H limits of 5 and 7 a constant value of 2·2 is found for the ratio $[HPO_4'']/[C_6H_{11}O_5 \cdot O \cdot PO_3'']$.

Large-scale preparations of pure glucose 1-phosphate as the crystalline potassium salt are described, and by the action of purified phosphorylase on glucose 1-phosphate large amounts of a polysaccharide resembling potato starch have been obtained. The product shows the typical granules of native starch when viewed under the microscope; but further examination shows certain points of difference from natural potato starch. For example, the synthetic product is sparingly soluble in water and rapidly retrogrades when in solution; again, the iodine colour is much more intense than that given by potato starch. A third point of difference was observed in relation to its degradation by the β-amylase of ungerminated barley. Natural starches normally degrade to about 60% of maltose and the residue consists of resistant α-amylodextrin. The enzymically prepared starch, however, allows the action of the β-amylase to proceed almost to completion, 95—100% of the preparation being converted into maltose. The synthetic product corre-

[5] *Proc. Roy. Soc.*, 1940, B, 129, 174.

sponds thus most closely to the amyloamylose [6] fraction of starch. Much interest thus attaches to further investigation of the enzyme mechanisms involved in these remarkable transformations and to constitutional studies on the synthetic polysaccharide, which are now proceeding.

X-Ray comparisons between the natural and the synthetic starch are discussed by W. T. Astbury, F. O. Bell, and C. S. Hanes [7] in a recent note. The A-, B-, C-, and V-powder photographs correspond to wheat starch, potato starch, a mixture of the two, and to alcohol-precipitated starch respectively.[8] The only difference observable between the photographs of potato starch and the synthetic starch is that the former is very slightly sharper. A further curious point was discovered in that amyloamylose precipitated by alcohol after preparation by electrophoresis gave the V-photograph, whereas the synthetic starch still gave the B-photograph after precipitation with alcohol. A re-examination of the conditions governing the production of the different types of X-ray photograph may throw further light on the relation between the various types of starch. It is not clear at present whether different photograph types are due to differences in phosphorylases or, as seems more probable, in the method of crystallisation, i.e., preparation of the starches. The probability of the latter explanation is indicated by the fact that A-, B-, or C-photographs may be obtained from the same starch at different temperatures of deposition.[9]

A number of well-known factors influence the rate of breakdown of starch by enzymes and the nature of the products. It has recently been shown that comparatively mild treatment of starch prior to diastatic action leads to a much greater degradation than is possible with untreated starch. Thus, R. H. Hopkins, E. G. Stopher, and D. E. Dolby [10] describe the separation of starch into amylopectin and amyloamylose by electrophoresis, the starch having been previously treated in one of two ways. In some experiments the starch was finely ground in order to rupture the granules; in others the starch was made directly into a paste and dispersed at 120°. By alternate redispersion and electrophoresis the amylopectin fraction yields high proportions of amyloamylose, and the latter is far more completely degraded by barley diastase, but at a slower rate, than the untreated starch. The conversion into amyloamylose

[6] M. Samec, Z. physiol. Chem., 1936, **236,** 103.

[7] Nature, 1940, **146,** 558.

[8] J. R. Katz, "Die Röntgenspektrographie usw.," Berlin and Wien, 1934.

[9] J. R. Katz and J. C. Derksen, Z. physikal. Chem., 1933, A, **165,** 228.

[10] J. Inst. Brew., 1940, **46,** 426.

may reach yields as high as 80% if dispersion is carried out above 100°; the product reverts on standing to a substance which behaves towards diastase as does the starch from which it is obtained.

In recent years some doubt and minor controversy have arisen with reference to the effect of the particular buffer solution employed on the activity of enzymes. Not only has the nature of the buffer been held to affect the activity, but it has been suggested that ionic strength is an important factor. Experiments designed to investigate these points in the case of taka-diastase are described by G. A. Ballou and J. M. Luck.[11] Using a starch substrate, a temperature of 30°, and a series of buffers of an ionic strength of 0·05N, they found that the optimum p_H, in respect of saccharogenic action, was 5·1 for formate, acetate, propionate, butyrate, valerate, phenylacetate, and succinate buffers. A slight shift to p_H 5·4 was observed for buffers containing phthalate or citrate. Where the enzyme was employed at the optimum p_H or at a reaction on the alkaline side of this value, variation in the anion of the buffer was without effect on the relative activity; but on the acid side of the optimum, marked differences were observed with varying anions.

Employing the usual methods of methylation and end-group assay, E. G. E. Hawkins, J. K. N. Jones, and G. T. Young [12] have found that the starch present in unripe bananas conforms structurally to the usual pattern in that the repeating unit consists of a chain of about 24 glucose residues. Similarity to rice starch [13] is further indicated by the close resemblance of the course of disaggregation in the two cases. Disaggregation was discussed in last year's Report [14] and is effected in methylated starches by hydrolysis with oxalic acid in a mixture of methyl alcohol and water. The hydrolysis takes place at the bonds between the repeating units, since, although products of lower molecular weight are obtained, the chain length of the repeating unit remains unchanged.

A more rapid method of assay of the end group in methylated starch is reported by S. Peat and J. Whetstone.[15] The method involves acetolysis of methylated starch by acetyl bromide in cold chloroform. Treatment of the product with methyl alcohol gives a mixture of methyl glucosides from which the tetramethyl glucoside is separated by distillation. The removal of the end group is selective and rapid, the tetramethyl derivative separating within five minutes of the commencement of the reaction.

Pectin, Mucilages, etc.—Constitutional studies on pectic acids continue and are involving the preparation and characterisation of

[11] *J. Biol. Chem.*, 1940, **135**, 111.   [12] *J.*, 1940, 390.
[13] E. L. Hirst and G. T. Young, *J.*, 1939, 1471.
[14] *Ann. Reports*, 1939, **36**, 272.   [15] *J.*, 1940, 276.

a number of derivatives of galacturonic acid exhibiting a fructo-furanose structure. Among these may be mentioned the methyl ester of 2 : 3 : 5-trimethyl β-methylgalacturonoside, which has been synthesised by S. Luckett and F. Smith.[16] In the course of investig-ations on citrus pectic acids, these authors [17] have also isolated the methyl ester of 2 : 3-dimethyl methylgalacturonoside and have suggested that citrus pectic acid is built up of pyranose residues of galacturonic acid joined by 1 : 4 α-glycosidic linkages. Osmotic pressure measurements on the methyl ester of methylated pectic acid appear to indicate a small molecule of about 13 units.

Using such sources as Tuso pith and sliced radishes, S. Onon [18] has isolated pectic substances on the usual lines and with the usual properties. A method of extraction is of interest, however, in that the extractive is boiling water containing copper sulphate. By this means it is claimed that pectins are obtained of a snow-white colour, and of a galacturonic acid and methoxyl content much higher than those normally obtained. The resulting pectin is considered to be a polymerised trimethyl tetragalacturonic acid and contains no araban or galactan residues.

Valuable contributions to the study of jelly formation by pectin have been made by C. L. Hinton,[20] who suggests that pectins may be regarded as complex mixtures of carboxylic acids whose con-stituents cannot be separated at present. However, they may be studied from a physicochemical standpoint and much information has been gained in this way. Thus the effect of variation of a number of factors, such as concentration of pectin and of other soluble substances present, the p_H of the mixture, the effect of de-esterification of pectin by pectase or alkali, on the strength of the jelly has been studied. Electrolytic dissociation of pectin was investigated and the " constant " was found to diminish as neutral-isation with alkali became more complete ; but there was no import-ant change in the constant for pectins boiled for one hour or de-esterified enzymically, or by citric acid. Jelly formation involves only those molecules of pectin which are in the un-ionised condition, and these must reach a certain solubility or saturation limit varying with the total solids concentration of the mixture. The strength of a particular jelly with a given buffer salt was found to be propor-tional to the amount of non-ionised pectin above the solubility limit. The ratio of jelly strength to the amount of jellying substance differed for different pectins. This theory of jelly formation has been elaborated and has explained many of the phenomena observed, especially those relating to the effect of p_H. Encouraging results

[16] J., 1940, 1114.   [17] Ibid., p. 1106.
[18] Bull. Sch. Agric., Taihoku, 1940, 1, 1.   [20] Biochem. J., 1940, 34, 1211.

may be expected to follow from this investigation, which is probably the first attempt to treat in ordered and mathematical fashion the mass of diffuse and often contradictory data which have tended to obscure rather than clarify the problem.

The constitution of the mucilage of carrageen moss (*Chondrus crispus*) is the subject of investigation by T. Dillon and P. O'Colla,[21] who submit the mucilage to acetolysis in the usual manner and obtain, after removal of acetyl groups, two polysaccharides which appear to be galactans. These correspond to those found by P. Haas *et al.*,[22] in that one is soluble in water and one soluble only in hot water. The latter workers were unable to isolate the polysaccharides, which they showed to exist as calcium salts of ethereal sulphates. The carbohydrate hydrolysis products appeared to be chiefly galactose and fructose, but Dillon and O'Colla were unable to confirm the latter, although indications were obtained that fructose was present in solution on deacetylation.

In another communication on the same subject, E. G. V. Percival and J. Buchanan [23] confirm the work of Haas and criticise the later findings of Dillon and O'Colla on the grounds that their method of acetolysis involved considerable degradation of the polysaccharides, all constituents except galactose being lost. This indicates that galactose must be contained in the most resistant portions of the molecule, but the complexity of the latter is indicated by other hydrolysis products, which appear to include glucose, a pentose, and possibly a ketose. The probable configuration of the molecule is responsible for the difficulties observed in acetolysis and methylation.

A product of the nature of a polysaccharide and hydrolysing largely to xylose is reported for the first time from the red alga, *Rhodymenia palmata*, by V. C. Barry and T. Dillon.[24] The alga is immersed in dilute hydrochloric acid for 24 hours and from the resulting viscous solution a white precipitate is obtained with alcohol. The precipitate yielded crystalline xylose in hydrolysis with dilute nitric acid. A similar treatment on the case of *Dilsea edulis* produced a substance which appeared to be similar to the mucilages from other marine algæ. It was an ethereal sulphate, contained no xylose, and was oxidisable to mucic acid.

Attempts have been made from time to time to isolate polysaccharides similar to naturally occurring plant gums by the action *in vitro* of bacteria, normally associated with a particular plant, on sucrose in artificial media. The work of E. A. Cooper and J. F.

[21] *Nature*, 1940, **145**, 749.
[22] *Biochem. J.*, 1921, **15**, 469; 1922, **16**, 578; 1929, **23**, 425.
[23] *Nature*, 1940, **145**, 1020.
[24] *Ibid.*, 1940, **146**, 620.

Preston has been recorded in these Reports [25] and the subject is renewed by R. R. Lyne, S. Peat, and M. Stacey,[26] who find that polysaccharides of the levan type are formed by *B. megatherium*, *Bact. pruni*, and *Bact. prunicola* under the above conditions. So far, polysaccharides comparable with the gums have not yet been produced. Examination of the hydrolysed methylated levans showed that each could be represented by a chain of 10—12 fructose units, and in this respect they resembled the levans produced by *B. subtilis*. Differences in properties among the levans are thought to be due to varying degrees of aggregation of the repeating unit. A practical point of some importance is the observation that the polarimetric rotation of the acetates in chloroform solution depends on the water content of the reaction mixture and this probably explains discrepancies in results by previous workers.

Hemicelluloses.—Although much analytical investigation of the cell-wall of plant tissues has been conducted, in most cases it is the mature material which has been examined, and little work by comparison has been expended on the developing tissue. Such investigation would prove of value in the formulation of theories of the origin of the constituents of mature tissue. A. Allsopp and P. Misra [27] have studied the common ash, the common elm and Scotch pine, whose tissue they divide into three " fractions " : the cambium, together with the differentiating xylem; newly formed wood; and mature sapwood. The composition of the first-named fraction showed similarities with that published for other young tissues. A high pectin content is characteristic of the young cell wall and in this and the lower lignin : cellulose ratio the cambium and differentiating elements contrast chiefly with the mature wood. Even after vessel differentiation is complete there are small changes in composition, involving the loss of pectin, increase in encrusting pentosans and in the resistance of the lignin constituents. Theories of origin of the constituents of mature cell-walls based on the observed fact that, for instance, a fall in pectin concentration during lignification indicates that the lignin arose from the pectin, must be treated with reserve, since a change in concentration is no indication of a change in total quantity present. The same remark applies to the suggestion that hemicelluloses are derived from pectin.

Osmotic pressure and viscosity studies on a number of polyoses of wood by E. Husemann [28] indicate a wide range of molecular size, the particles responsible for the development of osmotic pressure being molecules and not molecular aggregates. Degree of polymerisation is of the order of 150—220 units in the case of xylans,

[25] *Ann. Reports*, 1938, **35**, 378.   [26] *J.*, 1940, 237.
[27] *Biochem. J.*, 1940, **34**, 1078.   [28] *Naturwiss.*, 1939, **27**, 595.

from wheat straw and beechwood, mannan from spruce and arabo-galactan from larch. These values are small compared with that for beech cellulose, which is given as not less than 1500. The degree of polymerisation is unaltered on conversion of the products into acyl derivatives. On the basis of viscosity measurements it is thought that, whereas the mannan and xylans comprise long chains, the arabogalactan molecule consists of multi-branched chains.

M. H. O'Dwyer,[29] continuing her investigations on the hemi-celluloses of oak wood, has found that the transition from sap-wood to heart-wood as shown by preparation of hemicellulose A from the two types involves definite constitutional changes in this com-ponent. The greater proportion of the carbohydrate residues in the molecule are anhydroxylose and these are combined with uronic acid and methoxyaldobionic acid residues, the former predominating in the hemicellulose of the sap-wood, the latter in that of the heart-wood. A further difference was also noticed, in that the hemicellulose preparations from sap-wood all gave the iodine blue coloration typical of starch, whereas the heart-wood preparations gave no iodine colour. Although at this stage glucose was not found as a hydrolysis product of the sap-wood preparations, it was suggested that the blue coloration was due to the presence of anhydroglucose residues in the hemicellulose.

In a later communication O'Dwyer [30] reports that hemicellulose A may be split up into two polysaccharide fractions by the action of taka-diastase and in addition some 10% of the glucose has been obtained from sap-wood hemicellulose A. The action of water at 100° effects a similar scission, but glucose is not split off. The presence of glucose is seen to be the only difference between the hemicellulose A of sap- and heart-wood,[31] the polysaccharide frac-tions after prolonged hydrolysis with taka-diastase being identical. The complete hydrolysis involves production of two parts of a soluble polysaccharide and three parts of xylose. The molecule of the poly-saccharide appears to consist of six anhydroxylose units combined with one methyluronic anhydride unit.

In the latest paper [32] to date similar results are obtained with hemicellulose B. Again the sap-wood hemicellulose only gives the iodine coloration and contains anhydroglucose units. The products of fission under the action of taka-diastase appear to be the same for all the hemicelluloses examined. Hemicelluloses have been pre-pared by E. Anderson, M. Seeley, W. T. Stewart, J. C. Redd, and D. Westerbreke [33] from various hardwoods before and after chlorin-

[29] *Biochem. J.,* 1934, **28**, 2116.   [30] *Ibid.,* 1937, **31**, 254.
[31] *Ibid.,* 1939, **33**, 713.   [32] *Ibid.,* 1940, **34**, 149.
[33] *J. Biol. Chem.,* 1940, **135**, 189.

ation.   Their results confirm much that has been suggested by
W. G. Campbell,[34] M. H. O'Dwyer, and others with reference to the
origin of hemicelluloses in woods.   Two of the woods examined,
lemon wood and black locust sap-wood, contained starch and all
of the hemicelluloses from these woods gave a blue or pink coloration
with iodine.   These hemicelluloses appear to contain anhydroglucose
groups in the xylan chain, and may possibly represent intermediate
products in the transformation of starch or its degradation products
into hemicelluloses.   The hemicelluloses of birch wood and black
locust heart-wood did not contain starch, gave no typical colour
with iodine, and were differentiated from the other hemicelluloses
in chemical composition, since the xylan groups were combined with
a monomethylated uronic acid.   The probable number of xylan
groups in the chain varies with different hemicelluloses and appears
to approximate to 19 in the largest molecules and 8 in the smallest.
The carboxyl group of the uronic acid may be involved in attach-
ment of the hemicellulose to some other substance of the cell-wall.
This might explain the fact that, although the hemicellulose is not
extractable from the wood by hot water, it is nevertheless somewhat
soluble in hot water after extraction with sodium hydroxide.

Hemicelluloses prepared by the usually recognised methods are
reported from a number of sources, including oat hulls,[35] wheat-
straw,[36] and lucerne hay.[37]   Those obtained from wheatstraw con-
sist mainly of the B-fraction with small amounts of A and C.   The
hydrolysis products include xylose, arabinose, and possibly a methyl
derivative of glucuronic acid ; the xylose predominates.   The same
remarks apply to the hemicellulose of lucerne hay.

The methods adopted in the pre-treatment of materials employed
for the preparation of hemicelluloses have given rise to some contro-
versy, a principal bone of contention being the use of alcoholic
sodium hydroxide for the removal of lignin.   This method was used
by F. W. Norris and I. A. Preece,[38] but was shown later by the latter
author [39] to involve some loss of furfuraldehyde-yielding material.
The procedure was also criticised by A. G. Norman [40] on similar
grounds.   Nevertheless, S. Angell and F. W. Norris [41] found that
in the pre-treatment of the flowers of the hop, no such loss could be
observed after treatment with alcoholic soda, and they suggested
that the effect of alcoholic soda depended on the material under

[34] *Biochem. J.*, 1935, **29**, 1068.
[35] P. W. Krznarich, *Cereal Chem.*, 1940, **17**, 457.
[36] H. D. Weike and M. Phillips, *J. Agric. Res.*, 1940, **60**, 781.
[37] M. Phillips and B. L. Davis, *ibid.*, p. 775.
[38] *Biochem. J.*, 1930, **24**, 59.   [39] *Ibid.*, 1931, **25**, 1304.
[40] *Ibid.*, 1935, **29**, 545; 1937, **31**, 1579.   [41] *Ibid.*, 1936, **30**, 2159.

investigation.   The subject is again opened by I. A. Preece,[42] who employed teak sawdust as the raw material, and showed that there is definite loss of furfuraldehyde-yielding material when the wood is submitted to either alcoholic or aqueous soda extraction.   The extracted hemicelluloses themselves were not stable under these reagents.   The author concludes that pre-treatment with alcoholic soda does reduce the lignin content of subsequent preparations of hemicellulose, but the disadvantage of the treatment outweighs the advantages.   The choice of extractive must depend on the material and on the purpose in view in the preparation of the hemicellulose. Alcohol extraction may be employed in some cases, or alcoholic soda treatment in the cold, as employed by H. W. Buston [43] and A. G. Norman.[40]

Plant Proteases.—The isolation of papain in crystalline form has been achieved by A. K. Balls and H. Lineweaver,[44] who precipitated papaya latex successively with ammonium sulphate and sodium chloride at suitable concentrations and p_H in the presence of sodium cyanide.   The crystals were usually obtained in fine needles, which changed on long standing in water to elongated hexagonal plates. Analysis showed that the enzyme was of a protein nature, containing 15·5% of nitrogen, 1·2% of total sulphur, and 1% of cysteine sulphur. A molecular weight of about 30,000 was indicated by osmotic pressure measurements and by the evidence of the ultra-centrifuge.   The enzyme was only sparingly soluble in dilute saline solutions, but soluble in 70% alcohol.   The isoelectric point was at p_H 9.   The presence of an activator such as cyanide or cysteine was essential for the preparation of crystals of high activity and such activity corresponded to a maximum value per unit of protein nitrogen for all crystals, although prepared in different ways.

The presence of sulphydryl groups as necessary for papain activity is thus again indicated by the preceding work on crystalline papain. Activation-inhibition reactions of a group of similar plant proteases are investigated by D. M. Greenberg and T. Winnick,[45] who employ the bromelin of pineapples; solanain from the horse-nettle, *Solanum clœagnifolium*; a new protease from the latex of milkweed, *Asclepias mexicana*; and a protease from another milkweed, *Asclepias speciosa*.   In accordance with a recent suggestion it is proposed to use the suffix " ain " for new plant proteases, and for present purposes the last two enzymes are designated *asclepain m* and *asclepain s*.   All the enzymes with the exception of solanain show reactions which suggest that they are all related to papain, the presence of a sulphydryl group being necessary for activity.   Sola-

[42] *Biochem. J.*, 1940, **34,** 251.   [43] *Ibid.*, 1934, **28,** 1028.
[44] *J. Biol. Chem.*, 1939, **130,** 669.   [45] *Ibid.*, 1940, **135,** 761.

nain is unaffected by oxidising or reducing agents or reagents which react with sulphydryl groups. It is not a papainase and it is probable that phenolic groups may be essential for its activity as indicated by inactivations produced by nitrous acid and keten. There is some evidence also that the papainases may require phenolic in addition to sulphydryl groups.

p_H–Activity curves for the different enzymes, obtained with denatured hæmoglobin and ovalbumin as substrates, indicate an optimum p_H with hæmoglobin of 6·5—8·5, and with ovalbumin of 7—7·5. The character of the curve has been shown to depend more on the electrochemical nature of the enzymes than on the degree of dissociation of the substrates.[46]

In a third communication [47] the authors discuss the kinetics of the action of the enzymes, and determine the Michaelis constants in each case. In all cases the intermediate compound of enzyme and substrate consisted of equimolecular proportions of enzymes and protein. The heat inactivation of asclepain m and solanain followed the course of a first-order reaction and these enzymes closely resembled papain and bromelin in their high critical thermal increments.

Growth Substances.

Higher Plants.—The mechanism of the pea test for auxin has been further investigated by F. W. Went,[48] who finds that the curvature of split etiolated pea stems under the action of the auxin is due to a loss of sensitivity of the tissues bordering the wound. This loss of sensitivity is essential before auxin effect will take place, and is of the nature of a preparatory action, which is independent of p_H and may be effected by substances which lack growth-promoting activity. The dual aspect of auxin action is again referred to by F. W. Went,[49] who distinguishes two phases in the action of indolyl-acetic acid on etiolated pea stem cuttings. There is an initial effect which causes a redistribution of rhizocaline, and such effect is brought about by phenylacetic acid, which is not in itself a growth promoter; the later effect is induced only by indolylacetic acid and its homologues and appears to involve the activation of accumulated rhizocaline.

K. V. Thimann and C. L. Schneider [50] have shown that the relative activities of growth substances as compared with indolyl-acetic acid vary with the species of plant treated and with different methods of treatment in the same species. They record results with a number of growth substances, and employ straight growth tests

[46] *J. Biol. Chem.*, 1940, **135**, 775.   [47] *Ibid.*, p. 781.

[48] *Bull. Torrey Bot. Club*, 1939, **66**, 361.

[49] *Amer. J. Bot.*, 1939, **26**, 24.   [50] *Ibid.*, pp. 328, 792.

with *Pisum*, and a new method of curvature test wherein *Avena* coleoptiles are slit longitudinally and thus grown in auxin solutions. It is claimed that the test is some 30 times as sensitive as the agar block method, and that indolylacetic acid may be detected in concentration as low as 0·01 µg. per litre.

That auxin is present in bound form which is only slowly split up by an action which is probably enzymic is suggested by F. Skoog and K. V. Thimann.[51] They find that extraction of auxin with ether is complete only after some months and it is assumed that this is due to the slow hydrolysis of auxin in the bound form. That the mechanism may be enzymic is indicated by the fact that addition of trypsin preparations accelerates the extraction according to the particular preparation employed.

D. M. Bonner [52] has shown that acids of similar molecular structure have the same activity in growth reactions, dependent on p_H. Thus, the acid-induced curvature in split sections of pea stems results from an increase in active auxin produced after a change in the internal p_H of the cut surface. Dissociation measurements on a number of acids such as *cis*-cinnamic, indolyl-acetic, -propionic, and -butyric, and naphthylacetic show that equimolar concentrations of the acids have the same activities. The effect of p_H in respect of the growth reaction of *Avena* coleoptiles has been examined by J. V. Rakitin and L. M. Jarkovaja,[53] who find that increasing acidity over the range 6·32—3·8 enhances the auxin effect. Observations were made with an acetate buffer and with oxalic, citric, malic, and sulphuric acids.

N. H. Grace [54] has compared the activity in inducing rooting of cuttings shown by acids of the ω-naphthyl-aliphatic series, and finds activity for acids up to and including the hexoic acid. Acids having an even number of carbon atoms in the side chain have a greater activity than those with an odd number. In experiments on rooting of cuttings of *Lonicera tartarica*, indolylbutyric acid was most effective; indolylacetic and indolylpropionic acids showed less activity, and 5-methylindolylpropionic and indolylvaleric acids no action at all.

A. E. Hitchcock and P. W. Zimmerman [55] have examined the combined effect of mixtures of root-inducing and other substances and find that in a number of cases the mixtures are more effective than the separate components. Such mixtures frequently give greater numbers of roots, a higher percentage of rooted cuttings and

[51] *Science*, 1940, **92**, 64.   [52] *Bot. Gaz.*, 1938, **100**, 200.
[53] *Compt. rend. Acad. Sci., U.R.S.S.*, 1939, **23**, 952.
[54] *Canadian J. Res.*, 1939, **17**, C, 247, 373.
[55] *Contr. Boyce Thompson Inst.*, 1940, **11**, 143.

concomitant phenomena associated with large amounts of growth
substances.   Mixtures of indolyl-acetic and -butyric acids, and of
naphthyl- and phenyl-acetic acids with vitamins B_1 and B_6 and
ethylene were used.   It appears that the vitamins have no root-
inducing function in themselves, but act rather as root formation
activators.

It has been recognised for a long time that the concentration of
heteroauxin applied to the plant is somewhat critical, and that in
general higher concentrations not merely have little effect, but may
actually inhibit those effects which in lower concentrations are
promoted.   This finds support in experiments by Y. Hwang and
H. L. Pearse,[56] and by L. Duhamet.[57]   The former found that dilute
indolylacetic acid had little effect on oat and bean seedlings, and
that concentrations higher than 2 parts per million retarded growth.
Indolylacetic acid is evidently only a growth stimulator when
natural auxin is deficient.   The latter worker, employing extremely
low concentrations of indolylacetic acid, finds no effect with the
lowest, double the growth rate with a slightly less dilute solution, and
inhibition above a certain concentration.   Growth of roots of
Lupinus albus was observed in these experiments, and the small
amounts necessary to induce the auxin effect may be gauged when
it is stated that the best response was obtained with solutions of
10^{-11} normality.

Growth substances applied in vapour form were found to give the
same characteristic responses as when applied as aqueous solutions,
by P. W. Zimmermann, A. E. Hitchcock, and F. Wilcoxon.[58]
Similar experiments with vapours and solutions of growth substances
were later described by P. W. Zimmermann and A. E. Hitchcock,[59]
who examined 54 substances, including 26 reported for the first time.
All produced formative effects, although these differed in character
with the substance used.   It was notable that the more active sub-
stances employed in vapour form produced emanations from the
treated plants which affected their neighbours.   After a period of one
hour from exposure to the vapour, when carbon dioxide production
fell below that of controls, the production for the next five hours
exceeded that of the controls.   The same authors also compared the
efficiency of application of root-inducing substances as dusting
powders and in solution.   The two methods appear to have about
the same efficiency, but it was found that in the case of application
in a talc dusting powder, the talc itself had some beneficial influence,
in part due to the improvement in water relationships and in part

[56] *Ann. Bot.*, 1940, **4**, 31.   [57] *Compt. rend.*, 1939, **208**, 1838.
[58] *Contr. Boyce Thompson Inst.*, 1939, **10**, 363.
[59] *Ibid.*, pp. **481**, **461**.

possibly due to the fact that talc appears to contain a physiologically active ingredient, which could be extracted by chloroform.

Further investigation [60] of the traumatin (wound hormone) isolated by J. English, J. Bonner, and A. J. Haagen-Smit [61] has shown it to be Δ^1-decene-1 : 10-dicarboxylic acid, and the name traumatic acid has been given. The acid promotes wound periderm formation in potato and inhibits germination in seeds of tomato. In this respect decanedicarboxylic acid and sebacic acid were found to be about half as active as traumatic acid.

A new growth substance is reported by S. C. Bausor,[62] who has found that naphthoxyacetic acid and its sodium and potassium salts induce typical responses when applied in lanoline paste. The effects were recorded in detail in the case of root primordia of tomato plants.

A plant growth inhibitor was discovered by W. S. Stewart, W. Bergren, and C. E. Redemann [63] in cotyledons of radish plants, and a similar substance is reported by R. H. Goodwin [64] in ethereal extracts of maize meal and bean shoots; further confirmation of the existence of substances which inhibit growth, or at least mask the action of auxin, is provided by R. Snow [65] by the isolation of a water-soluble substance from pea leaves soaked in ether.

Yeast.—The final elucidation of structure and synthesis of pantothenic acid has been reported.[66] The high structural specificity of pantothenic acid is indicated as the result of biological examination of amino-acid analogues of the acid carried out by H. H. Weinstock, E. L. May, A. Arnold, and D. Price.[67] Esters of aspartic acid, alanine, lysine, and β-aminobutyric acid were prepared and condensed with αγ-dihydroxy-ββ-dimethylbutyric acid—the non-nitrogenous moiety of pantothenic acid. None of the synthetic analogues was active, although the close relationship of the amino-acids mentioned to β-alanine is sufficiently obvious.

E. E. Snell, R. E. Eakin, and R. J. Williams [68] have utilised the growth response of *Sacch. cerevisiæ* in presence of β-alanine and vitamin B_6 to determine minute amounts of biotin in natural materials such as autolysed liver, whey solids and cane molasses, which are among the richest sources of biotin. The latter is thought to be an α-amino-acid. A similar biological method of assay applied to pantothenic acid is described by D. Pennington, E. E. Snell, and R. J. Williams,[69] who utilise the response of *Lactobacillus casei* ε.

[60] *Science*, 1939, **90**, 329; *J. Amer. Chem. Soc.*, 1939, **61**, 3434.
[61] *Ann. Reports*, 1939, **36**, 369.
[62] *Amer. J. Bot.*, 1939, **26**, 415, 733.
[63] *Science*, 1939, **89**, 185.
[64] *Amer. J. Bot.*, 1939, **26**, 130.
[65] *Nature*, 1939, **144**, 906.
[66] See this vol., p. 226.
[67] *J. Biol. Chem.*, 1940, **135**, 343.
[68] *J. Amer. Chem. Soc.*, 1940, **62**, 175.
[69] *J. Biol. Chem.*, 1940, **135**, 213.

The requirements of yeast for the recognised bios substances are known to vary with the strain of yeast. Further confirmation of this is forthcoming as the result of recent work by R. J. Williams, R. E. Eakin, and E. E. Snell,[70] who also note that the necessity for these substances appears to diminish after long incubation. They also report the presence in liver extracts of additional unknown stimulants, in support of an earlier paper by E. F. Pratt and R. J. Williams [71] in which it was stated that the respiration and growth of yeast are stimulated to a much greater extent by liver extract than by any other known stimulant. Pantothenic acid not only exerts a stimulating effect on growth and respiration of living yeast but has been shown to enhance fermentation by dialysed yeast maceration juice. Suggestions that liver extract contains a yeast stimulant find support from the work of B. Alexander and Y. Subbarow,[72] who have obtained an acetone extract from liver which is active as a bios substance but appears on biological test to contain a substance different from any of those at present recognised as yeast growth stimulants. It is stable to heat and to acid hydrolysis and to some extent to alkaline hydrolysis, and is soluble in organic solvents. It is precipitated by phosphotungstic acid and unaffected by nitrous acid at room temperature.   F. W. N.

9. INDUCED GLYCOSIDE FORMATION IN PLANTS.

The full significance of glycosides in higher plants is still far from being understood. It has long been considered that the glycosides represent a detoxication mechanism in the plant analogous to the glucuronides excreted by animals when foreign substances are absorbed. The natural aglycones in plants may be said, on this view, to be toxic by-products of metabolism held in an immobilised state because the plant has no excretory system. It has now been shown by L. P. Miller [1] that a variety of plants will form glycosides from certain foreign substances which had previously [2] been shown to be physiologically active. This gives experimental support for the view that in the plant glycoside formation is a detoxication mechanism, as is the formation of glycuronides in animals. At present the results cannot be considered directly in relation to the natural glycosides, but the experimental methods used have over-

[70] *J. Amer. Chem. Soc.*, 1940, **62**, 1204.

[71] *J. Gen. Physiol.*, 1939, **22**, 637.   [72] *J. Biol. Chem.*, 1940, **135**, 341.

[1] *Contr. Boyce Thompson Inst.*, 1938, **9**, 425; 1940, **11**, 271; *Science*, 1940, **92**, 42.

[2] F. E. Denny, *Amer. J. Bot.*, 1926, **13**, 118; *Contr. Boyce Thompson Inst.*, 1937, **8**, 473.

come former difficulties and open a wide field for further investig-
ation.   Ethylene chlorohydrin, one of the substances found to break
the dormancy of tubers, is converted by the living tissue into
β-2-chloroethyl-d-glucoside.   The same plant was shown to convert
o-chlorophenol into β-(o-chlorophenyl)gentiobioside.   Chloral hydr-
ate was converted into β-trichloroethylgentiobioside, reduction to the
alcohol taking place as in animals.   Thus it appears that the foreign
substance influences the type of glycoside subsequently obtained
from the plant.   That the foreign aglycones are literally immobile
in the plant is shown by the fact that on the subsequent growth of
treated corms no traces of the induced glycoside can be found either
in the tops or in the new corm.   R. H.

10. Growth Factors for Bacteria.

Accessory food factors playing a part in the nutrition of the
animal [1] and of yeasts [2] have recently been dealt with in these
Reports; the subject of bacterial vitamins will now be reviewed.

Most of the vitamins known to function in the animal and all
those so far found necessary for any variety of yeast have been
found necessary for one bacterium or another; on the other hand,
several substances have been shown to be necessary constituents in
the growth of bacteria but have not yet been shown to function in
the animal.   It may be recalled, however, that pantothenic acid was
proved to be a necessary factor in the nutrition of certain yeasts
before it was proved to function in the animal.

It is well known that heterotrophic bacteria differ widely in their
food requirements.   Many organisms isolated from soil can be
cultivated in serial subculture on media consisting of inorganic salts,
deriving their nitrogen requirements from ammonia and their carbon
from carbohydrates or salts of simple organic acids.   Others need
complex media consisting of protein digests with or without carbo-
hydrate; for still more exacting organisms, blood, ascitic fluid, liver
extract, yeast autolysate or egg yolk may be necessary; it is mainly
the last type which provides the material for vitamin studies.
According to the view put forward by P. Fildes,[3] organisms which
require a large selection of compounds from which to build up their
cell material have lost a number of synthetic powers which more
primitive organisms possess; this he believes is due to prolonged
cultivation in an environment where they are surrounded by a rich
assortment of molecules which they are able to use " ready made,"
as a result of which they lose synthetic powers.   Thus highly para-

[1] *Ann. Reports*, 1939, **36**, 340.   [2] *Ibid.*, p. 369.
[3] *Proc. Roy. Soc. Med.*, 1934, **28**, 79.

sitic organisms resident in the animal body have more exacting food requirements when isolated and grown in culture than have most of their near relatives living in soil. Even non-parasitic organisms such as the lactic fermenters have in many cases lost the power to synthesise essential molecules, such as riboflavin or pantothenic acid, which are present in milk.

The inability to synthesise substances essential for the building of cell material is carried to greater lengths among bacteria than in the animal world. Not only is the list of accessory food factors already known for bacteria longer than that for the animal, but many strains must be supplied with a formidable selection of amino-acids, some in only very low concentration. For such organisms these amino-acids cannot logically be distinguished in function from vitamins, though for convenience it is proposed to exclude them from this Report.

In investigating the nutritional requirements of an exacting organism, two methods of approach are possible. A medium may be built up from simple known constituents until it is adequate for the growth of the organism. This method is possible only if the requirements of the organism are comparatively simple. The second method, and the one more likely to attain success, is to start with a medium—however complicated—fully adequate for the growth through serial subculture, and then, by fractionating the various constituents, eliminate unnecessary material until the simplest group adequate has been attained. If this still contains unknown constituents, it may be possible to replace them by known vitamins; otherwise the active substances must be isolated and their constitution determined. When this has been achieved, two concentrations of the new factor should be given; the minimum concentration which supports visible growth and the minimum required for maximum growth through serial subculture.

The first method is exemplified by work of Fildes on *Proteus*, the second by the work of Mueller on *C. diphtheriæ*.

Proteus.—This organism differs from those with the simplest requirements in only one particular, that is, it grows ærobically on inorganic salts and ammonium lactate if nicotinic acid only is added $(0 \cdot 1 \ \mu g./ml.)$.[4] Nicotinic acid is among the most widespread requirements of bacteria and it is possible that the ability to synthesise it is readily lost. Within the *Proteus* group, however, two degrees of synthetic disability are found, all *P. morganii* strains requiring in addition pantothenic acid, which produces detectable growth in $0 \cdot 001 \ \mu g./ml.$ and optimal growth in $0 \cdot 005 \ \mu g./ml.$[5]

    [4] P. Fildes, *Brit. J. Exp. Path.*, 1939, **19**, 239.
    [5] M. J. Pelczar and J. R. Porter, *Proc. Soc. Exp. Biol. Med.*, 1940, **43**, 151.

The second or analytical method for determining the growth requirements of a microbe is exemplified in the classical studies of J. H. Mueller [6] on the exacting, H.Y. strain of *C. diphtheriæ*. This organism was cultivated on a medium consisting of (A) a salt mixture, (B) Liebig's extract, 7·5 mg./ml.; (C) tryptophan, 0·1 mg./ml.; (D) an acid hydrolysate of caseinogen, 10 mg./ml. The growth obtained in 60 hours was equivalent to 0·2 mg. of nitrogen/ml. and it was the aim of the study to replace this medium by one of known composition giving an equal bacterial crop in the same time. (A), (B), and (C) being kept constant, (D) was adequately replaced by a mixture of amino-acids with ethyl alcohol as additional source of energy; the acid hydrolysate of casein being now replaced by known compounds free from contaminating vitamins, (B) was replaced by liver extract, from which were isolated two constituents both necessary for the growth of the organism, *viz.*, nicotinic acid,[7] active in 0·1 μg./ml., and β-alanine,[8] active in 0·1 μg./ml.; a third substance necessary was present in the liver extract, but was actually isolated from cow's urine; this was pimelic acid, active in 0·005 μg./ml.[9] The effect of the last is duplicated by synthetic pimelic acid, but not by any other member of the series tried. These three substances in the concentrations stated completely replaced the liver extract. These findings were confirmed by English workers [10] for all strains of *C. diphtheriæ mitis* and most of the *gravis* strains tested. Some still more exacting strains of the latter type failed to grow on this medium, but grew when liver extract was added. From the latter a concentrate was prepared which could be replaced by pantothenic acid [11] (αγ-dihydroxy-ββ-dimethylbutyrylalanide). We have then in this group two grades of synthetic disability; the majority of strains can use either β-alanine or pantothenic acid, the exacting *gravis* strains require pantothenic acid supplied as such.

The Lactic Fermenters.—This group of organisms, isolated from milk and cheese, forms another group of varying vitamin requirements. Orla-Jensen *et al.*[12] first showed that milk which had been shaken with activated charcoal no longer supported the growth of many of these strains, but that when riboflavin together with the

[6] *J. Bact.*, 1935, **29**, 515.

[7] J. H. Mueller, *J. Biol. Chem.*, 1937, **120**, 219.

[8] J. H. Mueller and S. Cohen, *J. Bact.*, 1937, **34**, 381.

[9] J. H. Mueller, *J. Biol. Chem.*, 1937, **119**, 121.

[10] W. C. Evans, W. R. C. Handley, and F. C. Happold, *Brit. J. Exp. Path.*, 1939, **20**, 41, 396.

[11] E. T. Stiller, J. C. Keresztesy, and J. Finkelstein, *J. Amer. Chem. Soc.*, 1940, **62**, 1779.

[12] S. Orla-Jensen, N. C. Otte, and A. Snog-Kjaer, *Mem. Acad. Roy. Sci. Lettres Danemark*, 1936, **6**, no. 5; *Zentr. Bakt. Par.*, II, **94**, 434, 452.

material eluted from the charcoal was added to the deficient milk, the growth rate attained on untreated milk was almost reached. Later workers have more precisely determined the requirements of this group; [13] the medium consisted of bactopeptone, salts, cystine, and glucose. This was rendered free from riboflavin by exposing the peptone to light in alkaline solution; four strains grew on the riboflavin-free medium (*Str. lactis, L. arabinosus, L. pentosus,* and *Leuconostoc mesenteroides*); *L. delbrückii, L. casei, L. gayoni,* and *B. lactis acidi* grew only when riboflavin (0·1 μg./ml.) was added. It is noteworthy that all lactic fermenters tested contain riboflavin whether it is supplied in their growth medium or not.[14]

The activity of various synthetic flavins was tested and compared with that of the natural product obtained from milk; only those containing ribose were active and none equalled riboflavin.[15]

		Activity.
I.	6 : 7-Dimethyl-9-*d*-1'-ribityl*iso*alloxazine (riboflavin) ...	100
II.	6-Methyl-9-*d*-1'-ribityl*iso*alloxazine	50
III.	7-Methyl-9-*d*-1'-ribityl*iso*alloxazine	78
IV.	7-Methyl-6-ethyl-9-*d*-1'-ribityl*iso*alloxazine	75
V.	6 : 7-Dimethyl-9-*d*-1'-arabityl*iso*alloxazine	Inactive
VI.	6 : 7-Dimethyl-9-*l*-1'-arabityl*iso*alloxazine	,,
VII.	6 : 7-Dimethyl-9-1'-sorbityl*iso*alloxazine....................	,,
VIII.	9-*ll*-Arabityl*iso*alloxazine	,,
IX.	9-(*dl*-Ribityl)-5 : 6-benzo*iso*alloxazine	,,
X.	6 : 7 : 9-Trimethyl*iso*alloxazine (lumiflavin)	,,
XI.	6 : 7-Dimethylalloxazine (lumichrome)	,,
XII.	Riboflavin tetra-acetate	,,

It is noteworthy that substitution in the 6:7-positions leaves some activity and that the ribityl group is essential and cannot be replaced by other sugars or by methyl.

The effectiveness of the synthetic flavins for bacterial growth is closely paralleled in animal studies, only I, II, III, and IV being active in rat growth tests.[16]

The necessity for pantothenic and nicotinic acids for some members of the group was demonstrated as follows. A medium consisting of an acid hydrolysate of bactopeptone supplemented by salts, sodium acetate, cystine, and riboflavin failed to support growth unless liver extract was added. The latter was fractionated, and a concentrate obtained active in 0·003 μg./ml. This was subsequently found to owe its activity to pantothenic acid. Some strains grew poorly on this medium, and required in addition nicotinic acid (0·05 μg./ml.). Strains requiring pantothenic acid were *B. lactis*

[13] E. E. Snell, F. M. Strong, and W. H. Peterson, *Biochem. J.*, 1937, **31**, 1789; *J. Bact.*, 1939, **38**, 293; *J. Amer. Chem. Soc.*, 1938, **60**, 2825.

[14] F. Schütz and H. Theorell, *Biochem. Z.*, 1939, **295**, 246.

[15] E. E. Snell and F. M. Strong, *Enzymologia*, 1939, **6**, 186.

[16] Kühn *et al.*, *Ber.*, 1937, **70**, 2560.

acidi, *L. arabinosus*, *L. pentosus*, *L. delbrückii*, *B. brassicæ* and *Str. lactis*. Those requiring nicotinic acid in addition were *L. casei* and *L. arabinosus*.[17]

The strain of *Str. lactis* isolated from silage and originally known as *Bact. acetyl choline* (Keil), in addition to factors already mentioned, requires adermin (vitamin B_6), 3-hydroxy-4 : 5-bis(hydroxymethyl)-2-methylpyridine.[18] This compound is also required by *Str. hæmolyticus* (see p. 440).

The Dysentery Group.—S. A. Koser *et al.*[19] have shown that nicotinic acid is essential for a number of dysentery bacilli (*Flexner, Hissy, Strong,* and other unspecified strains). These were sown in a basal medium of fifteen amino-acids, glucose, and salts ; growth was completely negative on the basal medium, but full rapid growth occurred on the addition of nicotinic acid, 0·1 μg./ml. ; 0·04 μg./ml. gave slower growth and a visible effect was obtained with 0·01 μg./ml.

The Pasteurella *Group.*—A number of organisms of the *Pasteurella* group have been found to require nicotinamide and pantothenic acid (0·1 μg./ml. was used in both cases) ; the former was replaceable by coenzyme I, but β-alanine did not replace pantothenic acid ; this case resembles that of the exacting strains of *C. diphtheriæ gravis.*[20]

The Staphylococci.—The growth requirements of this group of organisms are high. Aerobically they grow on peptone water, but it is clear that this does not function only as a source of amino-acids, for when it is replaced by (say) an acid digest of caseinogen plus tryptophan, tyrosin, and cystine, no growth occurs, unless extract of meat or yeast is added. From the latter (in the form of marmite) two active fractions, both necessary, were obtained,[21] the one replaceable by nicotinic acid or amide (0·2 μg./ml.) or by diphospho-pyridinedinucleotide, the other by aneurin (0·02 μg./ml.).

The organism can use the two basic components of aneurin if these are provided separately, *viz.*, 4-amino-5-aminomethyl-2-methyl-pyrimidine (0·002 μg./ml.) and 4-methyl-5-β-hydroxyethylthiazole (about 0·01 μg./ml.).

The specificity for the thiazole base appears to be complete, closely related compounds tried being quite inactive even at concentrations 100 to 1000 times that used for the acceptable compound. Thiochrome, for example, will not replace aneurin and 4-methyl-

[17] E. E. Snell, F. M. Strong, and W. H. Peterson, *J. Amer. Chem. Soc.*, 1938, **60**, 2825.

[18] E. F. Möller, *Z. physiol. Chem.*, 1938, **254**, 285.

[19] S. A. Koser, A. Dorfman, and F. Saunders, *Proc. Soc. Exp. Biol. Med.*, 1938, **38**, 311.

[20] S. Berkman, F. Saunders, and F. A. Koser, *ibid.*, 1940, **44**, 68.

[21] B. C. J. G. Knight, *Biochem. J.*, 1937, **31**, 731.

thiazole does not replace 4-methyl-5-β-hydroxyethylthiazole. The organism is, however, less specific towards the pyrimidine group, the following substitutes for the aneurin base being active in approximately the same concentration, *viz.*, 4-amino-5-thioformamido-methyl-2-methylpyrimidine and 4-amino-5-aminomethyl-2-methyl-pyrimidine; inactive, however, were 4-hydroxy-5-hydroxymethyl-2-methylpyrimidine, 4-hydroxy-5-aminomethyl-2-methylpyrimidine, and 4-amino-2-hydroxypyrimidine (cytosine).[22]

The anaerobic metabolism of *Staph. aureus* is different from its aerobic metabolism; in the former case it derives its energy mainly from amino-acids; anaerobically from glucose and pyruvic acid. In the latter case an additional factor is required, *viz.*, uracil (2 : 6-dihydroxypyrimidine), which is active in 1—5 μg./ml. Related bases were inactive, *viz.*, 5-methyluracil (thymine), 4-methyluracil, 1 : 3-dimethyluracil, 1 : 3 : 4-trimethyluracil, 2-thio-5-methyluracil, barbituric acid, cytosine, and *iso*cytosine.[23]

Str. haemolyticus.—Growth of this organism failed on a medium consisting of bactopeptone to which were added cystine, glucose, and a formidable list of bacterial vitamins. The addition of meat extract supplied the material lacking, which was subsequently identified as glutamine, which supported full growth at 30 μg./ml.[24] A number of related compounds, including glutamic acid, aspartic acid, and asparagine, are inactive.[25]

Two other factors for this organism were discovered by treating the bactopeptone with alkali, which resulted in an inactive medium. Growth was then obtained on the addition of riboflavin (0·1 μg./ml.) and pantothenic acid (1·0 μg./ml.).[26, 27] Finally, vitamin B_6 was shown to be necessary by growing the organism on a selection of amino-acids (replacing protein hydrolysate), riboflavin, and pantothenic acid plus an aqueous extract of liver. The active part of the last was adsorbed on lead sulphide and eluted, and the eluate adsorbed on and eluted from fuller's earth. The concentrate thus obtained was active in 1 μg./ml. and could be replaced by vitamin B_6.[28] This was confirmed by an alternative procedure.[29]

The Clostridia.—The requirements of the *Clostridia* (spore-bearing strict anaerobes) are notoriously high as to both vitamins and amino-

[22] B. C. J. G. Knight, *Biochem. J.*, 1937, **37**, 966.

[23] G. M. Richardson, *ibid.*, 1936, **30**, 2184.

[24] H. McIlwain, P. Fildes, G. P. Gladstone, and B. C. J. G. Knight, *ibid.*, 1939, **33**, 223.

[25] H. McIlwain, *ibid.*, p. 1942.

[26] B. L. Hutchings and D. W. Woolley, *J. Bact.*, 1938, **38**, 285.

[27] H. McIlwain, *Brit. J. Exp. Path.*, 1939, **20**, 330.

[28] B. L. Hutchings and D. W. Woolley, *Science*, 1939, **90**, 42.

[29] H. McIlwain, *Brit. J. Exp. Path.*, 1940, **21**, 25.

acids and few cases have been worked out in detail.   *Cl. sporogenes* furnished an early example of a bacterial vitamin.[30]   The active substance was found in yeast, moulds, bacteria, and urine ; a highly concentrated preparation from yeast was active in 0·02 μg./ml.   It is an acid substance forming a soluble barium salt and a methyl ester distilling at 80—100°/0·001 mm.[31]   It awaits further identification and is probably necessary for other members of the *Clostridia*.

The butyl fermenters display definite vitamin requirements and work on this group is in a state of active progress.   *Cl. butylicum* grows on a synthetic medium containing asparagine and glucose as the only organic compounds and needs in addition only biotin.[32, 33, 34] It can be used, therefore, as the test organism for the presence of this substance, $1·3 \times 10^{-5}$ μg./ml. being detectable.   The following table shows growth as measured by the turbidimeter ; 0 represents the uninoculated culture, 100 complete opacity.

Biotin, μg./ml.	Growth measured by turbidimeter.
0·000000	2·2
0·0000133	10·2
0·0000266	29·0
0·000053	54·0
0·00010	75·0
0·00020	88·0
0·00066	94·0
Liver conc., μg./ml.	
0·0133	39·0
0·0333	60·0
0·0666	79·0
0·1332	94·0
0·2664	94·0
0·6660	96·0

The closely related *Cl. acetobutylicum* requires in addition some factor or factors obtained from yeast.[35, 36]   Moreover, the study of these fermenters is complicated by the fact that some still unidentified factor (or factors) modifies the course of the fermentation as well as the growth.[36, 37]

The Hæmophilus *Group.*—The vitamin requirements of this group have not been determined recently enough to be considered here and will therefore be only briefly stated.   Two factors were found necessary in cultivating these organisms, the X factor obtained from

[30] B. C. J. G. Knight and P. Fildes, *Brit. J. Exp. Path*, 1933, **14**, 112.

[31] A. M. Pappenheimer, *Biochem. J.*, 1935, **29**, 2055.

[32] F. Kögl and B. Tönnis, *Z. physiol. Chem.*, 1936, **242**, 43.

[33] E. E. Snell and R. J. Williams, *J. Amer. Chem. Soc.*, 1939, **61**, 3594.

[34] W. H. Peterson, L. E. McDaniel, and E. McCoy, *J. Biol. Chem.*, 1940, **133**, LXXV.

[35] C. Weizmann and B. Rosenfeld, *Biochem. J.*, 1939, **33**, 1376.

[36] A. E. Oxford, J. O. Lampen, and W. H. Peterson, *ibid.*, 1940, **34**, 1588.

[37] C. Weizmann and B. Rosenfeld, *loc. cit.*

blood and the V factor from animal or plant tissues or other bacteria. The former was identified as hæmatin, and the latter as diphospho-pyridinenucleotide (coenzyme I), replaceable by the triphospho-derivative (coenzyme II). When grown anærobically, the former can be dispensed with and it has been suggested that it is required, in part at any rate, for the synthesis of catalase, which is unnecessary in anærobic life where hydrogen peroxide is not formed. It has recently been claimed that cysteine can replace hæmatin in ærobic growth; this is regarded as evidence that the hæmatin is required for the synthesis of catalase; in the presence of cysteine hydrogen peroxide would be reduced and catalase rendered unnecessary. Further details of this work are promised.[38]

Nicotinic acid or amide cannot replace the diphosphopyridine-nucleotide in this group, whereas organisms requiring the former can replace it by the latter (cf. the case of β-alanine and pantothenic acid in the *diphtheriæ* group).

Functions of Bacterial Vitamins.—Organisms which require a given vitamin can be used as delicate reagents for the detection of that substance in naturally occurring materials and for a rough quantit-ative assay during its isolation. *Str. hæmolyticus* or one of the exacting strains of *C. diphtheriæ gravis* can be used to determine the presence and approximate amount of pantothenic acid in a liver or yeast extract, the only alternative method involving prolonged animal feeding experiments; six days' work may thus replace six weeks'. It is fairly apparent that the vitamins shown to be neces-sary in the special strains which require them supplied in the medium are of wide-spread importance and exist also in other species which are able to make them for themselves. This can be shown by using extracts of non-exacting strains to supply the known requirements of exacting strains.

Some success has been achieved in determining the function of certain vitamins by the method first used by Lwoff and Lwoff. This consists in growing an organism requiring the vitamin in a medium containing it in a sub-optimal concentration. The organism so obtained is comparable with a vitamin-deficient animal and by a comparison of its enzyme systems with those of the normally grown organism it may be possible to show what chemical mechanism is deficient. Thus *H. parainfluenzæ* grown in sub-optimal amounts of coenzyme I was shown to have decreased powers of oxidising glucose, etc.; this power could be augmented by the addition of co-enzyme I to the reaction vessel. With the organism grown normally, the addition of coenzyme I does not affect the oxidation rate.[39]

[38] T. L. Snyder and R. H. Broh-Kahn, *Nature*, 1938, **142**, 153.
[39] A. Lwoff and M. Lwoff, *Proc. Roy. Soc.*, 1936, *B*, **122**, 360.

Washed suspensions of *Staph. aureus* grown in sub-optimal amounts of aneurin oxidise and dismute pyruvate at a lower rate than suspensions of organisms grown in optimal amounts of aneurin ; the rates in the former case are increased by the addition of aneurin to the reacting vessel, but the rates in the latter case are not affected.[40] The organisms grown in the aneurin-deficient medium are seen, therefore, to suffer from lack of cocarboxylase (aneurin diphosphate) and to display the same decreased ability to metabolise pyruvate as the tissues of the pigeon suffering from the same vitamin deficiency.

The following table indicates the vitamin requirements among bacteria, yeasts, and animal tissues :

	Bacteria.	Yeasts.	Animal.
Nicotinic acid	+	+	+
β-Alanine	+	+	
Pantothenic acid	+	+	+
Riboflavin	+	+	+
Adermin (vitamin B_6)	+	+	+
Aneurin	+		+
Uracil	+		
Asparagine	+		
Biotin	+	+	+
Sporogenes vitamin	+		
Coenzyme I	+		
Hæmatin	+		
Pimelic acid	+		

M. S.

11. NITROGEN METABOLISM OF BACTERIA.

Nitrogen Fixation.—The publication by A. I. Virtanen and T. Laine [1] of the experimental details of their work on the symbiotic nitrogen-fixing *Rhizobium* confirms the general scheme set out in the former's book [2] and collects the information appearing in various notes and abstracts.[3] It is claimed that nitrogen is fixed by the organism with the production of hydroxylamine, which then reacts with oxaloacetic acid produced by the host plant from carbohydrate, as follows :

$$N_2 \longrightarrow ? \longrightarrow NH_2 \cdot OH$$

$$\downarrow$$

$$HO_2C \cdot C(:NOH) \cdot CH_2 \cdot CO_2H \longrightarrow HO_2C \cdot CH(NH_2) \cdot CH_2 \cdot CO_2H$$

$$\uparrow$$

$$C_6H_{12}O_6 \longrightarrow HO_2C \cdot CO \cdot CH_2 \cdot CO_2H$$
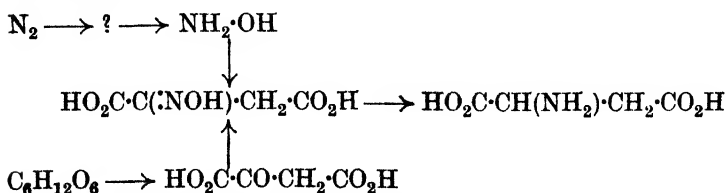
[40] G. M. Hills, *Biochem. J.*, 1938, **32**, 383.   [1] *Biochem. J.*, 1938, **32**, 412.

[2] A. I. Virtanen (1938), "Cattle Fodder and Human Nutrition," Cambridge University Press.

[3] A. I. Virtanen, *J. Soc. Chem. Ind.*, 1935, **54**, 1015; *J. Agric. Sci.*, 1937, **27**, 332; *Agric. Col. Sweden Ann.*, 1938, **5**, 429.

The evidence supporting this scheme, which is put forward by these workers, rests on the following points :

(1) The infected plant excretes *l*-aspartic acid into the medium around the roots.[4, 5]

(2) The aspartic acid is excreted only from roots infected with *Rhizobium*.[6]

(3) Oxaloacetic acid can be detected in the host plant.[7]

(4) The oximinosuccinic acid has been isolated and identified,[1, 8] but hydroxylamine itself has not been identified.

(5) Nitrogen fixation by free-living *Rhizobium* cultures has been observed in the presence of oxaloacetic acid.[9]

(6) The greater part of the nitrogen excretion which is not accounted for -by the aspartic acid consists of β-alanine,[10] and suspensions of *Rhizobium* will decarboxylate aspartic acid to form β-alanine.[11]

(7) In the presence of crushed pea plants, the amino-group of aspartic acid may be transferred to keto-acids such as pyruvic acid with the formation of α-alanine, etc.[12]

The conclusions of Virtanen have been criticised by P. W. Wilson,[13] who has reviewed the work of the Wisconsin school in this field.   His criticisms, published before the detailed description of Virtanen's work, are not completely justified now and are largely disposed of by the isolation of the oxime.[1]   Wilson has been unable to obtain significant nitrogen-fixation by the free-living *Rhizobium* cultures in the presence of oxaloacetic acid.   The Wisconsin workers have shown that, the plant and bacteria being treated as one system, the rate of nitrogen fixation is dependent upon the nitrogen pressure,[14] independent of the oxygen pressure over a wide range,[15] and specifically inhibited by hydrogen.[13]

Little advance has been made in our knowledge of nitrogen-fixation by the free-living *Azotobacter*.   A. I. Virtanen and T. Laine [16] have found aspartic acid as the chief product of excretion, but as this is much less marked than with *Rhizobium*, the study has not as yet been elaborated.   G. Endres [17] has found oximes formed by

[4] A. I. Virtanen and T. Laine, *Nature*, 1935, **136**, 756.

[5] *Idem, Suomen Kem.*, B, 1937, **10**, 32.

[6] A. I. Virtanen, von Hausen, Synnöve, and T. Laine, *J. Agric. Sci.*, 1937, **27**, 332.

[7] A. I. Virtanen and T. Laine, *Suomen Kem.*, B, 1938, **11**, 25.

[8] *Idem, Nature*, 1938, **142**, 165.

[9] *Idem, Suomen Kem.*, B, 1937, **10**, 24.

[10] *Idem, ibid.*, p. 2.   [11] *Idem, Enzymologia*, 1937, **3**, 266.

[12] *Idem, Nature*, 1938, **141**, 748.   [13] *Ergebn. Enzymforsch.*, 1938, **8**, 13.

[14] P. W. Wilson, *J. Amer. Chem. Soc.*, 1937, **58**, 1256.

[15] P. W. Wilson and E. B. Fred, *Proc. Nat. Acad. Sci.*, 1937, **23**, 503.

[16] *Suomen Kem.*, B, 1937, **10**, 2.   [17] *Annalen*, 1935, **518**, 109; 1938, **535**, 1.

Azotobacter growing in the presence of nitrate.   D. D. Woods [18] has shown that washed suspensions of *Cl. welchii* and *Bact. coli* (probably many other types) will reduce nitrate first to nitrite and then to ammonia in the presence of hydrogen and has brought forward good evidence that the reduction of nitrite proceeds through hydroxylamine.

A. S. Corbet and W. R. Wooldridge [19] have investigated the distribution of nitrogenous compounds in sewage and the changes that occur during the activated sludge process.   Confirming much earlier work on soil, their experiments indicate that the following interactions and changes can occur in the nitrogen cycle :

$$
\begin{array}{ccc}
NH_3 & \underset{d}{\overset{a}{\rightleftharpoons}} & \text{Organic N} \\
\downarrow b & & \nearrow \qquad \uparrow c \\
NO_2 & \xrightarrow{\qquad c \qquad} & N_2 \\
\downarrow b \uparrow c & & \\
NO_3 & &
\end{array}
$$
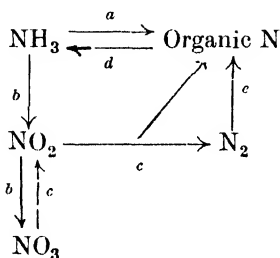
The particular course of the reactions followed varies according to the conditions which obtain, especially as regards the proportions of available carbonaceous matter and nitrogen present and the nature of the compound in which the nitrogen occurs.   The reactions indicated in the diagram are encouraged by the following chemical conditions :

(*a*) The presence of ammonia and assimilable carbon compounds.

(*b*) Ammonia present, but little or no assimilable carbon compounds.

(*c*) Assimilable carbon compounds present together with nitrite and/or nitrate as the most readily available source of nitrogen.

(*d*) Autolytic changes arising from the absence of nutrient materials.

(*e*) Fixation of nitrogen in the presence of assimilable nitrogen-free organic compounds and no readily available source of nitrogen other than free gas.

Activated sludges appear to contain the enzymes necessary to effect any of the above changes.

Amino-acid Metabolism.—G. M. Hills [20] has studied the amino-acid metabolism of certain pathogenic bacteria.   Gram-positive cocci contain an enzyme which attacks arginine to form ornithine and ammonium carbonate ; as neither citrulline nor urea appears to be an intermediate in the reaction, the enzyme has been named arginine

[18] *Biochem. J.*, 1938, **32**, 2000.

[19] *Ibid.*, 1940, **34**, 1015, 1026, 1036.   [20] *Ibid.*, p. 1057.

dihydrolase. Gram-positive bacteria produce no ammonia ærobic-
ally from other amino-acids with the exception of *Staphylococcus*,
which attacks serine and threonine. *Bact. typhosum* deaminates
serine, aspartate, threonine, and arginine ærobically, and *C.
diphtheriæ* appears to attack aspartate only. A. Janke and W.
Tayenthal [21] showed that glycine is oxidatively deaminated by
washed suspensions of *Bact. coli, Bact. vulgare, Ps. fluorescens,* and
Bac. mycoides : glyoxylic acid was isolated as the 2 : 4-dinitrophenyl-
hydrazone. A series of papers by P. Desnuelle *et al.*[22] has dealt with
the anærobic breakdown of cysteine and cystine by washed suspen-
sions of *Bact. coli*. Cysteine is broken down by an adaptive cystein-
ase, liberating ammonia and hydrogen sulphide in equimolecular
quantities. The reaction is partially inhibited by glucose and is
specific for the natural isomer. Cystine is reduced to cysteine before
further attack. The enzyme responsible for the breakdown of
cysteine by *Propionibact. pentosaceum* [23] differs from the cysteinase
of *Bact. coli* in being accelerated by the presence of glucose, showing
no optical specificity, and not requiring the presence of the substrate
during growth for its formation. The products of the breakdown
other than ammonia and hydrogen sulphide have not been reported.
C. E. Clifton [24] has shown that serine is disrupted anærobically by
washed suspensions of *Cl. botulinum* with the formation of ammonia,
carbon dioxide, acetic acid, and ethyl alcohol. He suggests that
pyruvic acid is formed as an intermediate.

The breakdown of $l(+)$-glutamic acid and $l(-)$-aspartic acid by
bacteria has been the subject of several investigations. E. Adler
and co-workers [25] have been able to extract the glutamic acid
dehydrogenase from suspensions of *Bact. coli* by a modification of
the method used previously by M. Stephenson [26] for the extraction
of lactic dehydrogenase. The extracted enzyme reduces methylene-
blue in the presence of glutamic acid and coenzyme II and evidence
is put forward to show that the dehydrogenation to iminoglutaric acid
is reversible. The reactions involved in the deamination of glutamic
acid are :

   (*a*) Glutamic acid + coenzyme $\rightleftharpoons$ Iminoglutaric acid + dihydro-
                                             coenzyme
   (*b*) Iminoglutaric acid + H_2O $\rightleftharpoons$ Ketoglutaric acid + NH_3
   (*c*) Dihydrocoenzyme + $\frac{1}{2}O_2$ $\rightleftharpoons$ Coenzyme + H_2O

[21] *Biochem. Z.,* 1937, **289,** 76.

[22] P. Desnuelle and C. Fromageot, *Enzymologia,* 1939, **6,** 80, 242, 387.

[23] P. Desnuelle, E. Wookey, and C. Fromageot, *ibid.,* 1940, **8,** 225.

[24] *Proc. Soc. Exp. Biol. Med.,* 1940, **43,** 588.

[25] E. Adler, V. Hellstrom, G. Gunther, and H. Euler, *Z. physiol. Chem.,*
1938, **255,** 14.

[26] *Biochem. J.,* 1938, **22,** 605.

J. R. Klein [27] has shown that washed suspensions of *Hemophilus parainfluenzæ* oxidise aspartic and glutamic acids with the liberation of ammonia and the formation of acetic acid according to the equations :

$$\text{Aspartic acid} + O_2 \longrightarrow CH_3 \cdot CO_2H + NH_3 + 2CO_2$$
$$\text{Glutamic acid} + 2\tfrac{1}{2}O_2 \rightleftharpoons CH_3 \cdot CO_2H + NH_3 + 3CO_2$$
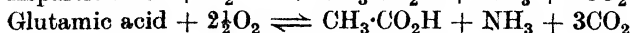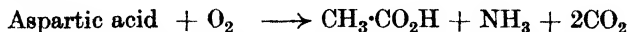
By a study of the metabolism of possible intermediate compounds, Klein has established the probable course of the oxidation. For aspartic acid the reaction proceeds : aspartic acid $\longrightarrow$ oxaloacetic acid $\longrightarrow$ pyruvic acid $\longrightarrow$ acetaldehyde $\longrightarrow$ acetic acid. The first and the last step require the presence of a coenzyme.

E. F. Gale [28] has shown that there are two mechanisms in *Bact. coli* which deaminate aspartic acid anærobically. One of the enzymes concerned is stable to toluene treatment and is the aspartase of J. H. Quastel and B. Woolf,[29] which deaminates aspartic acid to fumaric acid. The other enzyme is inhibited by toluene and requires the presence of a coenzyme, which can be replaced *in vitro* by adenosine. The two enzymes have been fractionated in a cell-free juice obtained from *Bact. coli* crushed in a bacteria-crushing mill designed by V. H. Booth and D. E. Green.[30] Since the fraction containing aspartase II also contains fumarase, the immediate product of the deamination process is not known. A. I. Virtanen and J. Erkama [31] claim to have shown the presence of two enzymes attacking aspartic acid in *B. fluorescens liquefaciens*, one producing fumaric acid and the other carrying out a hydrolytic deamination to form malic acid. If the latter statement is proved, it will be the first known case of biological hydrolytic deamination.

E. F. Gale and M. Stephenson [32] have continued their studies on factors affecting bacterial deamination. Washed suspensions of *Bact. coli* deaminate glycine, *dl*-alanine, and *l*(+)-glutamic acid ærobically and *dl*-serine and *l*(−)-aspartic acid anærobically. Anærobic growth conditions increase the formation of the anærobic deaminases and decrease that of the ærobic deaminases, whereas the presence of glucose during growth inhibits the formation of all deaminases studied to the extent of 85—95%. The activity of the serine deaminase varies greatly with the age of the culture and upon the condition of the organism, the presence of phosphate and a reducing agent being necessary to prevent this activity being lost on standing. J. W. Baker and F. C. Happold [33] have studied the groups essential to the tryptophan molecule for the production of

[27] *J. Biol. Chem.*, 1940, **134**, 43.
[28] *Biochem. J.*, 1938, **32**, 1583.
[29] *Ibid.*, 1926, **20**, 545.
[30] *Ibid.*, 1938, **32**, 855.
[31] *Nature*, 1938, **142**, 954.
[32] *Biochem. J.*, 1938, **32**, 392, 1583.
[33] *Ibid.*, 1940, **34**, 657.

indole from that molecule by *Bact. coli*. Up to the present no attempt to isolate or identify an intermediate substance in this breakdown has met with success. By studying the action of the cell-free tryptophanase preparation on a large number of tryptophan derivatives, they have obtained results which suggest that the breakdown to indole requires the following structural features : (*a*) a free carboxyl group, (*b*) an unsubstituted α-amino-group, (*c*) a β-carbon atom capable of oxidative attack. They tentatively suggest a type of breakdown involving " reductive fission " of the tryptophan molecule, but there is as yet no experimental evidence for this type of reaction.

The study of the amino-acid metabolism of the *Clostridia* (strict anaerobes) has been continued by several workers. D. D. Woods and C. E. Clifton [34, 35] have found that *Cl. tetanomorphum* utilises many amino-acids, causing the liberation of ammonia and hydrogen. The course of the breakdown of glutamic acid has been worked out in detail, the products being acetic acid, butyric acid, carbon dioxide, hydrogen, and ammonia. The same products in the same proportions are produced by the growth of an unidentified *Clostridium* growing on a glutamic acid medium and studied by H. A. Barker.[36] W. Kocholaty and J. C. Hoogerheide [37] have studied the dehydrogenation reactions carried out by *Cl. sporogenes* and have found that in certain cases amino-acid molecules can act as both hydrogen donators and acceptors, so that intramolecular reactions occur in which one molecule is oxidised and another reduced, thus forming a special case of the intermolecular oxidation–reduction reactions discovered by L. H. Stickland.[38] C. E. Clifton [39] has studied the amino-acid metabolism of *Cl. botulinum* and finds that it obtains its energy through " Stickland " reactions in a manner similar to that of *Cl. sporogenes*.

Amine Formation.—A. I. Virtanen and T. Laine [40] followed up their observation that *Rhizobium* decarboxylates aspartic acid with the formation of β-alanine by showing that *Bact. coli* produces cadaverine from lysine. Later [41] they found that *Rhizobium* will also decarboxylate glutamic acid to γ-aminobutyric acid. A. H. Eggerth *et al.*[42] have worked out an improved method for the estimation of histamine in bacterial cultures and A. H. Eggerth [43] has investigated the production of histamine by many species of

[34] *Biochem. J.*, 1937, **31,** 1774.   [35] *Ibid.*, 1938, **32,** 345.
[36] *Enzymologia*, 1937, **2,** 175.   [37] *Biochem. J.*, 1938, **32,** 437, 949.
[38] *Ibid.*, 1934, **28,** 1746.   [39] *J. Bact.*, 1940, **39,** 485.
[40] *Enzymologia*, 1937, **3,** 266.
[41] A. I. Virtanen, P. Rintala, and T. Laine, *Nature*, 1938, **142,** 674.
[42] A. H. Eggerth, R. S. Littwin, and J. V. Deutsch, *J. Bact.*, 1939, **37,** 187.
[43] *Ibid.*, p. 205.

organisms growing in culture. He has shown that many of the common inhabitants of the intestine will produce histamine, especially if glucose is present in the growth medium. By adjusting the medium p_H during growth, he showed that histamine is best produced if the p_H is low. Growth temperature also plays an important part, as some organisms produce more histamine if grown at a low temperature than at the normal 37°. All these results were obtained by bacteria growing in various media, so the effects studied may be produced by action on the growth of the organism rather than on the histamine-producing mechanism. The conditions under which bacteria produce certain amines by the simple decarboxylation of the corresponding amino-acids have been cleared up in a series of papers by E. F. Gale.[44] In the first case the conditions under which the organisms are grown are important; to obtain organisms possessing strongly active amino-acid decarboxylating enzymes, they must be grown under acid conditions in the presence of the free amino-acids. The most effective way of doing this is to grow the organisms in a tryptic digest of casein with 2% of glucose, the fermentation of the glucose producing the necessary low p_H. Organisms grown in this manner will decarboxylate certain amino-acids quantitatively to the corresponding amines at low p_H values, the optimum value in each case depending upon the amino-acid concerned. Thus washed suspensions of *Bact. coli* grown in glucose broth or in broth at p_H 5, the physiological limit of growth, will decarboxylate $l(+)$-arginine to agmatine optimally at p_H 4·0; $l(+)$-lysine to cadaverine at p_H 4·5; $l(+)$-ornithine to putrescine at p_H 5·0; $l(-)$-histidine to histamine at p_H 4·0; and $l(+)$-glutamic acid to γ-aminobutyric acid at p_H 4·0. Similarly, *Streptococcus fœcalis* quantitatively decarboxylates $l(-)$-tyrosine to tyramine at p_H 5·0. In all cases the product has been isolated from a simple mixture of washed suspension of organism, appropriate buffer, and amino-acid, the quantities so arranged that the decarboxylation has proceeded to completion. Good yields of pure product are obtained and it would seem that this biological method may be the best method for the large-scale production of some of these compounds. Several groups of organisms have been studied from this point of view and again the strictly anærobic group of *Clostridia* proves interesting : *Cl. welchii* decarboxylates histidine to histamine at the exceptionally low optimum p_H of 2·5—3·0, so in this case appreciable amounts of histamine are only produced *in vivo* when the organism grows in the presence of fermentable carbohydrate. Amongst other members of the group, *Cl. septique* decarboxylates ornithine to putrescine at p_H 5·5 and *Cl. ærofœtidum* forms tyramine from tyrosine at p_H 5·0. Many organisms, *e.g.*, most

[44] *Biochem. J.*, 1940, **34**, 392, 846, 853, and in the press.

strains of *Bact. coli, Bact. proteus, Cl. welchii, Cl. œrofœtidum, Cl. bifermentans*, decarboxylate glutamic acid to γ-aminobutyric acid. The distribution of the various decarboxylases shows that each enzyme is specific for one amino-acid.

G. M. Hills[45] has shown that certain *Streptococci* and *Staphylococci* will attack $l(+)$-arginine to produce ornithine by splitting off ammonium carbonate. This reaction is carried out by strains of *Strep. fœcalis* and consequently a symbiotic mixture of *Strep. fœcalis* and *Bact. coli* attacks arginine in an interesting fashion, the product of the attack at p_H 4·0 being agmatine and at p_H 5·5, putrescine, produced with ornithine as an intermediate substance.[46]

H. L. A. Tarr[47] has shown that the trimethylamine in putrid fish is produced by reduction of trimethylamine oxide by bacteria which possess an enzyme activating the trimethylamine oxide so that it can be reduced by any one of a number of dehydrogenase systems. Since only a few of the bacteria infecting putrid fish possess this enzyme, the trimethylamine production cannot be regarded as a measure of putrefaction.

Purine Metabolism.—M. Stephenson and A. R. Trim[48] have continued the investigations started by C. Lutwak-Mann[49] on the breakdown of adenylic acid and other adenine compounds by *Bact. coli*. Muscle adenylic acid is deaminated and dephosphorylated by *Bact. coli*, the dephosphorylation appearing to precede deamination. Adenosine is deaminated to inosine and the ribose is split off and fermented; the fermentation of ribose in adenosine is about 10 times as fast as that of free ribose. Adenine is slowly deaminated to hypoxanthine, the rate of deamination being increased some 6—7 times by the presence of adenosine—an effect similar to that found in the deamination of aspartic acid by aspartase II.[26]   E. F. G.

D. J. Bell.
J. F. Danielli.
E. F. Gale.
L. J. Harris.
R. Hill.
E. Kodicek.
J. R. Marrack.
A. Neuberger.
F. W. Norris.
M. Stephenson.

[45] *Biochem. J.,* 1940, **34,** 1057.   [46] E. F. Gale, *ibid.,* p. 853.
[47] *J. Fish. Res. Bd. Can.,* 1939, **4,** 367.
[48] *Biochem. J.,* 1938, **82,** 1740.   [49] *Ibid.,* 1936, **80,** 1405.

ANALYTICAL CHEMISTRY.

INTRODUCTION.

SINCE only a limited number of topics can be dealt with in detail each year, it is inevitable that much of the steady and solid growth of analytical chemistry, particularly along its well-developed branches, escapes attention. In this Report the analytical uses of distillation, colorimetry, fluorescence, and electrolytic methods have been chosen for detailed description. Though all the methods are basically physical, their analytical applications cover the whole field of chemistry.

In the analysis of organic substances, distillation, including azeotropic distillation, is frequently employed, possessing as it does the evident advantage that separation is effected without chemical change.

The technique of colorimetric analysis was summarised in the Report for 1936 and applications in Inorganic Chemistry received detailed treatment. The importance of traces of organic substances in biological fields and the recognition that colour reactions are among the most sensitive tests continue to stimulate the application of colorimetric methods. Examples of the utility of fluorescence methods in analysis have been given in the *Annual Reports* of the past decade, and it is clear that they must now be accepted as established analytical techniques.

The analytical uses of electrochemical phenomena are manifold, and the *Annual Reports* for 1933, 1934, and 1938 contained surveys of three branches, *viz.*, electrometric, oxidation–reduction potential, and polarographic methods, respectively. Electrodeposition, which is wholly inorganic in its scope, is now added to this group.

FRACTIONAL AND MOLECULAR DISTILLATION.

1. *General.*—Distillation has been defined as " the art of separating substances by the condensation of their vapours into liquid fractions of constant boiling point " (Thorpe's Dictionary, 4th Edn., Vol. 4, p. 34). Where only one component of a mixture is volatile, it can be obtained in a pure state by distillation if not decomposed in the process. Where all constituents of a mixture are volatile, generally, the more volatile constituents of the mixture increase in concentration in the vapour phase when the mixture is partially vapourised and equilibrium is established between the liquid and

the vapour phase; in such cases, by repeated distillations, or by fractionation, the mixture may be separated into its constituents. In the separation of pure substances from mixtures, the difficulties most likely to occur are due either to the presence of several components with nearly equal boiling points, or to the presence of one or more components in relatively small quantity. Improved fractionating columns have overcome these difficulties in some measure. A third difficulty, due to the formation of constant-boiling mixtures or azeotropes, cannot, however, be overcome in this manner.

To the chemist, distillation methods of analysis, in which the components are recovered unchanged, have advantages over chemical methods, in which one or more of the components are chemically altered. In many cases, too, a mixture which cannot be analysed readily by chemical methods may be separated into its components by fractionation through an efficient column. The ideal fractionation yields a series of sharply defined fractions, each distilling at a definite temperature; after each fraction has distilled, the temperature rises rapidly, no liquid being distilled as an intermediate fraction. In such an ideal fractionation, if temperature is plotted against volume of distillate, the graph obtained is a series of alternate horizontal and vertical lines resembling a staircase. A more or less sloping break indicates the presence of an intermediate fraction, and the amount of such fraction can be used as a criterion of the performance of different columns. As an example of the order of separation which can be obtained in the laboratory, a mixture of benzene, toluene, and xylene has been separated, practically quantitatively, into the three individual liquids.[1]

It is desirable to define some of the terms which are used in discussing fractionation columns. The *capacity* of a column is the measure of the amount of vapour and liquid which can be passed counter-current to each other in a column without causing it to choke or prime. The *efficiency* of a column is defined as the separating power of a definite length of column, and is measured by comparing the performance of the column with that calculated for a theoretically perfect plate column under similar conditions. For this comparison, it is necessary to distil a mixture in the column, and record certain liquid–vapour equilibrium data. The theoretical column which will give the same values is then calculated, and the number of theoretically perfect plates so determined is divided by the length of column employed to make the separation. The reciprocal of this efficiency is called the *height of equivalent theoretical plate*

(H.E.T.P.).[2] In comparing relative efficiencies of fractionating columns, the operating procedure requires to be standardised. A binary mixture whose liquid–vapour equilibrium data are known should be used, and the mixture should be one which is easily analysed by a simple determination. For instance, refractive index serves to evaluate mixtures of n-heptane and cyclohexane, benzene and carbon tetrachloride, or benzene and dichloroethane.

2. *Types of Column.*—Very long columns have been used in attempts to increase the separating power of a rectifying still. A 36·1 ft. packed laboratory glass column was used by J. H. Bruun and S. T. Schicktanz;[3] and subsequently M. R. Fenske, C. O. Tongberg, D. Quiggle, and D. S. Cryder[4] extended the length of a laboratory column to 52 ft. A very high degree of separation is obtainable in such columns, but their erection is rarely practicable.

The purpose of packing in a fractionating column is to effect as intimate a contact as possible between the ascending vapour and descending liquid without too great a reduction in capacity. A packing will not give a good separation unless it has a low H.E.T.P., nor will it prove satisfactory unless the capacity is adequate. A further requirement for packings which will give sharp separations is a low hold-up, *i.e.*, the packing must not retain or hold up a large quantity of the liquid being distilled.

A complete and extensive study of the relative fractionating efficiencies of analytical distillation columns has been made by W. J. Podbielniak,[5] using different types of columns and different column packings. Various factors influencing the separation of mixtures into sharp fractions have been considered, amongst them being the following :—

(i) *Time of distillation.* There is always an optimum time of distillation—in the case of the Podbielniak type of column about 3 hours—below which accuracy is sacrificed, and above which the slightly improved separation does not justify the extra time taken.

(ii) *Reflux ratio.* This is defined as the ratio between the number of mols. of vapour returned as refluxed liquid to the rectifying column and the number of mols. of final product, both per unit time. This should be varied according to the difficulty of fractionation, rather than be maintained constant. A high efficiency of separation requires a high reflux ratio.

(iii) *Hold-up of column.* The hold-up should be reduced to a minimum compatible with scrubbing effectiveness and an adequate

[2] W. A. Peters, junr., *Ind. Eng. Chem.*, 1922, **14**, 476.
[3] *Bur. Stand. J. Res.*, 1931, **7**, 851.
[4] *Ind. Eng. Chem.*, 1936, **28**, 644.
[5] *Ind. Eng. Chem. (Anal.)*, 1933, **5**, 119, 135, 172.

column capacity. Uniform, continuous, and geometrically symmetrical packings were found to be most suitable.

(iv) *Thermal insulation.* Slight heat losses completely disturb the delicate equilibrium of the column, and almost perfect thermal insulation is required to separate components boiling only a few degrees apart.

The fractionating columns described have a metal reflector-type vacuum jacket for thermal insulation at all temperatures from $-190°$ to $300°$, within which jacket any of a number of distilling tubes of different diameter may be inserted for the fractionation of gaseous or liquid samples. These distilling tubes contain spiral, continuous, uniform wire-coil packings. Using columns approximately 4 ft. long, Podbielniak has obtained in a single distillation lasting a few hours separations equal to those given by very tall columns operated at slow rates. The columns described are particularly suitable for the fractionation of hydrocarbon mixtures.

The construction and performance of three vacuum fractionating columns of the Podbielniak type with capacities of 5—500 g. suitable for the distillation of hydrocarbons, alcohols, and particularly esters have been described by A. Klem.[6]

A modified Dufton fractionating column has been used by W. J. Gooderham [1] for the analysis of hydrocarbon mixtures. A Dufton spiral is surrounded with a vacuum jacket which prevents the tendency of the spiral to choke at temperatures above $100°$, and enables extremely sharp fractionations to be obtained at high temperatures. The fractionating surface consists of a spiral of 10—12 mm. pitch—made by winding a soft copper wire around a stiff core (*e.g.*, nichrome)—which makes a tight, sliding fit in a strong tube of internal diameter 4·5 mm. The whole is enclosed in a silvered evacuated jacket.

Fenske and his co-workers [7, 8, 9] have studied various types of packing in fractionating columns. In investigations on columns of diameters from 0·6 to 2·0 in., the apparatus was worked with suitable liquid pairs, *e.g.*, benzene and carbon tetrachloride, under total reflux until equilibrium was established, the height of a theoretical plate equivalent to the packing being then determined. Efficiency was found to decrease with increase in diameter of the column; and corrosion of the packing had, in general, an adverse

    [6] *Nature*, 1938, **142**, 616.

    [7] M. R. Fenske, C. O. Tongberg, and D. Q. Quiggle, *Ind. Eng. Chem.*, 1934. **26**, 1169.

    [8] C. O. Tongberg, S. Lawroski, and M. R. Fenske, *ibid.*, 1937, **29**, 957.

    [9] *Idem, ibid.*, 1938, **30**, 297.

effect on performance.   The most efficient packings, which had a large surface area, and a high percentage free space, were one- and two-turn helices of wire or glass, and carding teeth $\frac{1}{8}''$ wide.   Owing to surface tension, which causes the condensate to coalesce on a dry packing but to spread uniformly on a wet one, the highest efficiency in the column was obtained when the packing was wetted by flooding just before the start of fractionation.   Fractionating columns with helix-type packings showed higher throughput and efficiency than columns containing the many other types of packing used.

The effect of packing in laboratory columns has been studied by other investigators.   A. R. Glasgow, junr., and S. T. Schicktanz [10] have studied the relationship between the efficiency (η), liquid hold-up (v), ball diameter (d), and total surface (a) in fractionating columns packed with glass, lead, and copper balls with diameters between 2 and 4 mm.   For a column of diameter 2·6 cm. packed with such balls, the thermal conductivity of the balls was without effect, and approximately $\eta \propto a/d^2$ and $v \propto a$.

Silicon carbide has been used as packing by H. J. Hall and G. B. Bachmann.[11]   Test data for mixtures of benzene and dichloro-ethane proved the efficiency of this type of packing, which has the advantage that it is not attacked during the distillation of organic bases, corrosive sulphur compounds, and unstable halides.   Fine-mesh wire-gauze packings, which gave an efficiency up to 20 plates per foot of column length, have been described by D. F. Stedman.[12]   L. B. Bragg [13] has described a laboratory column using a conical type of Stedman packing, and has recorded efficiency test data for a mixture of benzene and dichloroethane.   Columns equivalent to 200 theoretical plates can be built in a laboratory of average height.   M. L. Selker, R. E. Burk, and H. P. Lankelma [14] have described a 5-foot, efficiently insulated column, packed with close-fitting, multiple, concentric glass tubes, which has an efficiency of about 85 theoretical plates, and a small hold-up.   A fractionation column employing absorbents has been used in the separation of benzene and methyl alcohol.[15]

Enumeration of all the fractionating columns described in recent years is not possible in a limited space, but a few may be mentioned. Particulars of a jacketed, heat-insulated column about 2 metres long containing 100 bubble-cap plates (H.E.T.P. = 2 cm.) of the

[10] *J. Res. Nat. Bur. Stand.*, 1937, **19**, 593.
[11] *Ind. Eng. Chem. (Anal.)*, 1938, **10**, 548.
[12] *Canadian J. Res.*, 1937, **15**, B, 383.
[13] *Ind. Eng. Chem. (Anal.)*, 1939, **11**, 283.   [14] *Ibid.*, 1940, **12**, 352.
[15] R. J. Hartman and D. H. Jung, *Proc. Indiana Acad. Sci.*, 1937, **46**, 118.

type described by J. H. Bruun [16] have been given by J. H. Bruun and W. B. M. Faulconer.[17] The column has a separating power equivalent to about 70 theoretical plates, and very good separations of n-heptane (b. p. 98·4°) and toluene (110°), and of benzene (80·2°) and ethylene chloride (83·7°) were obtained. A similar and shorter column has been described by J. H. Bruun and S. D. West [18] for the distillation of low-boiling compounds, and in this column, n-propane of unusually high purity was prepared.[19] Various designs of fractionating columns have been given by J. H. Simons.[20] A small low-temperature rectifying column with capacity of *ca.* 5 c.c. of liquefied gas, which operates at constant pressure, and is suitable alike for purification and fractionation of small amounts of gases generated in reactions, and for liquids boiling at $- 130°$ to $- 50°$, has been described by the same investigator.[21] H. Vigreux [22] has described a fractionating column for distillation at atmospheric or lower pressures.

3. *Applications.*—Some interesting separations by fractionation have been made in recent years. J. R. Huffman and H. C. Urey [23] used a fractionating column made up with alternate stationary and rotating cones which provided a large reaction surface, to effect an approximately five-fold increase in concentration of the oxygen isotope of atomic weight 18. A few hundred c.c. of water containing 0·85% of $H_2^{18}O$ were obtained in this way. Rectification has been used in the separation of neon into its isotopes, and neon fractions with atomic weights 20·043 and 20·785 were obtained. A 38-fold enrichment of deuterium has been effected, and positive results obtained in the separation of the isotopes of oxygen.[24]

*cis*Butene-2 (b. p. 3·73°) and *trans*butene-2 (0·96°) have been separated by G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith, and W. E. Vaughan [25] in an all-glass column 5 m. long and 18 mm. in diameter packed with glass spirals of the type described by C. D. Wilson, G. T. Parker, and K. C. Laughlin.[26]

Distillation of decalin through a fractionating column at a pressure of 10 mm. of mercury, followed by several fractional crystallisations,

[16] *Ind. Eng. Chem. (Anal.)*, 1936, **8**, 224.

[17] *Ibid.*, 1937, **9**, 192.   [18] *Ibid.*, p. 247.

[19] M. M. Hicks-Bruun and J. H. Bruun, *J. Amer. Chem. Soc.*, 1936, **58**, 810.

[20] *Ind. Eng. Chem. (Anal.)*, 1938, **10**, 29.

[21] *Ibid.*, p. 648.   [22] *Ann. Falsif.*, 1938, **31**, 26.

[23] *Ind. Eng. Chem.*, 1937, **29**, 530.

[24] W. H. Keesom and H. Van Dijk, 7th Congr. intern. Froid, 1st Comm. intern. Rapports et Commun., June 1936, 103 ; W. H. Keesom, H. Van Dijk, and J. Haantjes, *Physica*, 1934, **1**, 1109.

[25] *J. Amer. Chem. Soc.*, 1935, **57**, 876.   [26] *Ibid.*, 1933, **55**, 2795.

has enabled W. F. Seyer and R. D. Walker [27] to isolate *cis*- and *trans*-decahydronaphthalenes, and a column of the Fenske type 35 cm. long and 1·5 cm. in diameter, packed with glass helices, has been used by M. L. Sherrill and E. H. Launspach [28] to purify *cis*-pentene-2.

4. *Microdistillation.*—The development of micromanipulation has resulted in attempts to achieve in microfractionation the degree of precision obtained in macro-work with carefully designed columns.

L. C. Craig [29] has described a column 100 mm. high for the distillation of 0·5—2·0 g. of material. The hold-up of the column is small, approximately 0·1 g., and in using a test mixture of benzene and carbon tetrachloride, a separation corresponding to approximately 8 theoretical plates was obtained. S. D. Lesesne and H. L. Lochte [30] have designed a semi-microfractionating column which uses a metal band 37·5 cm. long rotating at 1000 r.p.m. in place of packing. The apparatus can be used for quantities of 1—10 c.c., at atmospheric pressure, and the separation obtained was equivalent to 13 plates at total reflux. G. von Elbe and B. B. Scott [31] have described an apparatus for high-vacuum fractional distillation without gravitational reflux. The mixture to be fractionated (0·01—0·10 c.c.) is sealed in a long glass tube evacuated to 10^{-6} mm. of mercury around which a temperature gradient is maintained for a short distance by a thermostat system. The mixture tends to accumulate at the low-temperature end of the gradient, and by pulling the tube slowly and uniformly through the gradient towards the warm end, the mixture is made to distil continuously within the gradient. The method is illustrated by the separation of *p*- and *m*-xylene.

Other methods of microdistillation described include an apparatus with indented fractionation column suitable for quantities of 0·2—0·5 c.c.,[32] an apparatus for vacuum distillation of ≮0·5 g. of high-boiling fatty acids and their esters,[33] a distillation capillary for fractional distillation of low-boiling liquids in quantities as small as 0·02—0·10 c.c.,[34] and a microdistilling apparatus for fractionating under reduced pressure quantities of material of the order 0·5—2·0 g.[35]

5. *Molecular Distillation.*—In molecular distillation, the permanent gas pressure is so low (10^{-6} atm.) that it has very little influence on

[27] *J. Amer. Chem. Soc.*, 1938, **60**, 2125.   [28] *Ibid.*, p. 2562.
[29] *Ind. Eng. Chem. (Anal.)*, 1937, **9**, 441.
[30] *Ibid.*, 1938, **10**, 450.   [31] *Ibid.*, p. 284.
[32] J. W. Young, *Mikrochem.*, 1936, **21**, 133.
[33] E. Klenk, *Z. physiol. Chem.*, 1936, **242**, 250.
[34] A. O. Gettler and J. Fine, *Ind. Eng. Chem. (Anal.)*, 1939, **11**, 469.
[35] S. A. Shrader and J. E. Ritzer, *ibid.*, p. 54.

the speed of distillation, or even on whether distillation takes place or not.   The distillation velocity is then determined by the speed at which the vapour from the liquid being distilled can flow through the pipe connecting the still and condenser under the driving force of its own saturation pressure.   If the distance from the evaporating liquid to the condenser is made commensurate with or less than the mean free path of a molecule of distillate vapour in the residual gas at the same density and pressure, the molecules which leave the surface will for the most part not return.   A form of apparatus in which a cooled condensing surface is supported a few cm. above a shallow, heated pool of liquid, the whole enclosed in an evacuated chamber, offers the least hindrance to the flow of vapour from the evaporating to the condensing surface.   The rate of distillation is then determined by the rate at which the liquid surface is capable of producing vapour.   Where the evaporating liquid is a chemical individual, the rate of evaporation will be pc/s g. per sq. cm. per sec., p being the density of the saturated vapour at the given temperature, c the mean molecular velocity, and s the mean free path of a distillate molecule.   If the liquid is a mixture, the rate of evaporation of the rth component will be $p_r c_r/s$ g. per sq. cm. per sec.   The separation obtained in molecular distillation, therefore, depends on $p_r c_r$, unlike the separation obtained in ordinary distillation (where the vapour is in equilibrium with the liquid) which depends on p_r.   Since c_r is inversely proportional to the square root of the molecular weight and the value of p_r is in general greatest for constituents of least molecular weight, $p_r c_r$ is greatest for constituents of least molecular weight.   By molecular distillation, an improved separation can be obtained, e.g., of isotopes.   Indeed, the first application of molecular distillation was the separation of the isotopes of mercury.[36]   Subsequently, the method was applied to organic mixtures, e.g., to petroleum fractions by C. R. Burch,[37] and to paraffin wax by E. Washburn, J. H. Bruun, and M. M. Hicks.[38]   Molecular distillation is, indeed, the only method by which substances of high molecular weight can be distilled without decomposition, and it is a method by which it may be possible to avoid formation of constant-boiling mixtures.

An interesting account of the apparatus and methods used in molecular distillation has been given by K. C. D. Hickman.[39]   The apparatus described is suitable for distillation of cotton-seed or cod-liver oils, natural waxes, lubricating oils, synthetic polymerised material, etc.   Since under molecular distillation conditions, there

[36] J. N. Brönsted and G. von Hevesy, *Phil. Mag.*, 1922, [vi], **43**, 31.
[37] *Proc. Roy. Soc.*, 1929, **123**, *A*, 271.
[38] *Bur. Stand. J. Res.*, 1929, **2**, 467.   [39] *Ind. Eng. Chem.*, 1937, **29**, 968.

is virtually no foreign gas, evaporation takes place whenever there is a difference in temperature between distilland and condenser. Increase in the absolute temperature and in the temperature difference increases the rate of distillation, but there is no abrupt transition available for record as a boiling point. Hickman measures a property of the distilland analogous to the boiling point, *viz*., the " elimination curve," secured by plotting rate of elimination, *i.e.*, rate at which material appears in the receiver, against the increase in absolute distillation rate with temperature. The temperature of maximum elimination of the unknown is compared with that of " pilot " substances which are added in small amounts, *e.g.*, methyl-indigo, celanthrene-red 3B, etc. The " elimination curve " has been discussed mathematically by N. D. Embree.[40] Hickman[41] has distilled fish-oils in molecular stills, and has separated a vitamin-rich fraction evaporating below 190° and a mixture of glycerides evaporating at 190—250°. Two elimination curves for vitamin-*A* were found with maxima at 125° and 220°, probably corresponding to the free vitamin and to a mixture of its esters. Vitamin-*D*, likewise, showed maxima for the free vitamin (162°) and its esters (230—250°). Further work on the molecular distillation of vitamin-*D* has been published by K. C. D. Hickman and E. LeB. Gray,[42] and work on vitamins-*A* and -*D* by J. G. Baxter, E. LeB. Gray, and A. O. Tischer.[43] Molecular distillation has been applied to the concentration of the oil-soluble vitamins *A*, *D*, and *E*,[44] and the possibility of applying molecular distillation to large-scale industrial units has been considered by C. R. Burch and W. J. D. Van Dijck.[45] Molecular stills have been described for the concentration, fractionation, and purification of free fatty acids, sterols, vitamins, etc.[46]

6. *Azeotropic Mixtures*.—When a mixture of two or more components is distilled, the components normally separate in order of their boiling points. In many cases, however, the vapour pressure-composition curves show at particular concentrations maximum or minimum values corresponding respectively with minimum or maximum boiling points. The term " azeotropes " was applied by J. Wade and R. W. Merriman[47] to such mixtures. It is usual in such mixtures to find a minimum boiling point, and the mixture is said to exhibit positive azeotropism or azeotropism of the first

[40] *Ind, Eng. Chem.*, 1937, **39**, 975.   [41] *Ibid.*, p. 1107.

[42] *Ibid.*, 1938, **30**, 796.   [43] *Ibid.*, 1937, **29**, 1112.

[44] W. Jewell, T. H. Mead, and J. W. Phipps, *J. Soc. Chem. Ind.*, 1939, **58**, 56T.

[45] *Ibid.*, p. 39T.

[46] S. B. Detwiler, junr., and K. S. Markley, *Ind. Eng. Chem. (Anal.)*, 1940, **12**, 348.

[47] *J.*, 1911, **99**, 1104.

kind; negative azeotropism or azeotropism of the second kind is associated with a maximum boiling point. About 200 negative azeotropes are known.[48] The present discussion is restricted to positive azeotropism, but similar considerations hold for negative azeotropism. On distilling a mixture exhibiting positive azeotropism, the azeotrope distils over first, at constant boiling point, and any excess of either constituent remains in the still. It is possible by careful fractionation of such a mixture to separate (a) the azeotrope, and (b) one of the components, if present in excess. Lists of azeotropic mixtures are given in Sydney Young's " Distillation Principles and Processes " (London, 1922), in Maurice Lecat's book " La Tension de Vapeur de Mélanges de Liquides : L'Azéotropisme " (Brussels, 1935), and in other papers.[49]

Azeotropes may be separated into their constituents by chemical or physical methods. If one of the components is acidic, basic, or contains halogen, etc., chemical methods of analysis may be tried. Physical methods, however, are to be preferred, e.g., solubility of one of the components in a third liquid. If the qualitative composition of a binary (i.e., two-component) azeotrope is already known, the quantitative composition may be evaluated by comparing density, refractive index or other convenient property with the appropriate values for known synthetic mixtures. For example, azeotropic concentrations have been determined by density measurements accurate to a few parts per million [50] by using the twin pyknometer method of measuring density.[51]

Distillation methods may also be applied in several ways. A third substance may be added which forms either another binary azeotrope with one of the components or a tertiary azeotrope with both components, the new azeotrope having a lower boiling point than the original. On distillation, the new azeotrope distils first, leaving behind the other constituent or part of it. Such " third substances " may be selected from the tables given in Lecat's book.

R. Wright [52] has considered the case where there is addition of a third substance with selective action on one of the constituents. Addition of a relatively non-volatile material yields a distillate at first richer in the constituent in which the added substance is insoluble. The method was applied to the azeotrope n-propyl alcohol–water, which contains 28% of water. By adding 25%

[48] M. Lecat, *Ann. Soc. sci. Bruxelles*, 1934, **54**, *B*, 283.
[49] M. Lecat, *ibid.*, 1935, **55**, *B*, 253; 1936, **56**, *B*, 41, 221.
[50] M. Wojciechowski, *Nature*, 1938, **141**, 691.
[51] E. R. Smith and W. Wojciechowski, *Rocz. Chem.*, 1936, **16**, 104.
[52] *J.*, 1938, 1720.

by weight of potassium hydroxide to the azeotrope, in one dis-
tillation, material was obtained containing only 8% of water,
which, on fractionation, yielded the azeotrope and pure n-propyl
alcohol.

The reverse process, separation of liquids by first making them
form azeotropes with a third substance, is illustrated by the separ-
ation of butanes and butenes by distillation of their azeotropes
with sulphur dioxide, the butane azeotropes having lower boiling
points than any of the butene azeotropes.[53] In a similar manner,
(i) fusel oil may be analysed by fractionating the mixture of binary
azeotropes formed by the individual alcohols and carbon tetra-
chloride; and (ii) mixtures of aliphatic acids may be separated by
fractional distillation of the binary azeotropes which are formed
with benzene and toluene.[54] S. Young and (Miss) E. C. Fortey [55] de-
duced the empirical relationship for a positive azeotrope that the
ratio of the weight of constituent not in excess in the original
mixture to the weight of distillate below the mid-point, i.e., the
temperature mid-way between the boiling points of the two con-
stituents, is equal to the proportion of that constituent in the binary
mixture. Thus, if the proportion of that constituent in the azeotrope
is known, the composition of the original mixture can be deduced.

Azeotropes may be separated into their components by distillation
under reduced pressure. R. W. Merriman [56] showed that at
760 mm. pressure, the ethyl alcohol–water azeotrope contained
4·4% of water, whereas at 70 mm. pressure there was complete
separation of the two constituents. Other investigators have
considered the effect of pressure on azeotropes.[57] In the system
ethyl alcohol–benzene, E. Le. Borgne and M. Schmitt [58] have
studied the azeotropic concentration at pressures ranging from 89
to 1160 mm. of mercury.

Azeotropes may serve to identify unknown organic liquids if
they boil without decomposition at atmospheric pressure. The
method, which is described in Lecat's book, is to measure the
difference in temperature between the boiling point of one of a

[53] M. P. Matuszak and F. E. Frey, *Ind. Eng. Chem.* (*Anal.*), 1937, **9**, 111.

[54] (i) S. T. Schicktanz, A. D. Etienne, and W. I. Steele, *ibid.*, 1939, **11**, 421;
(ii) S. T. Schicktanz, W. I. Steele, and A. C. Blaisdell, *ibid.*, 1940, **12**, 320.

[55] *J.*, 1902, **81**, 717, 739; 1903, **83**, 45.

[56] *J.*, 1913, **103**, 628.

[57] A. A. Sunier and C. Rosenblum, *Ind. Eng. Chem.* (*Anal.*), 1930, **2**, 109;
W. Swientoslawski and B. Karpinski, *Compt. rend.*, 1934, **198**, 2166;
A. Bouzat and M. Schmitt, *ibid.*, 1934, **198**, 1923; W. D. Bonner and M. B.
Williams, *J. Physical Chem.*, 1940, **44**, 404; P. W. Schutz and B. E. Mallonee,
J. Amer. Chem. Soc., 1940, **62**, 1491.

[58] *Bull. Soc. sci. Bretagne*, 1936, **13**, 72.

series of standard liquids and that of the binary azeotrope formed by the standard and the unknown.

COLORIMETRIC ANALYSIS.

To the physicist, colorimetry relates to the process of complete spectrophotometric analysis or of determining a colour in terms of trichromatic coefficients, whereas to the chemist it generally refers to the process of comparing the colour of a medium with a standard colour, with the object of establishing the identity or the concentration of the substance responsible for the colour in the medium. Occasionally, the chemist finds it advantageous to employ the trichromatic system, as, *e.g.*, in measuring the colour of sugar products [1] and in defining a minimum blue colour which antimony trichloride shall produce with cod-liver oil in order that the latter shall conform with British Pharmacopœia requirements.[2] The principles underlying the selection of a correct terminology in relation to instruments and processes are discussed by M. G. Mellon.[3]

In colorimetric analysis, a photoelectric photometer or colorimeter has advantages of speed and accuracy over direct visual comparison methods, particularly when a number of determinations of the same substance by a particular colour reaction are being made, and the last few years have been marked by the production of a large variety of such instruments. It is of interest that thermopiles may be used in place of photocells, thereby permitting the construction of a thermoelectric absorptiometer.[4]

The investigation of a proposed colorimetric method now involves the determination of the spectral region in which light absorption is a maximum, and the provision of a light source corresponding with this region. The colour matching is then a matter of photometry. With the application of colour filters which transmit relatively narrow spectral bands, the gap between photoelectric colorimetry and photoelectric spectrophotometry is not large.[5] The fraction of incident light transmitted by the coloured medium is observed at time intervals to determine whether any changes occur as a result of any photochemical reaction or any incompleteness of the reaction which produces the coloured substance. The effective extinction coefficient under the optimum conditions and then the applicability of Beer's law are determined.[6] The

[1] E. Landt and H. Hirschmüller, *Z. Wirts. Zuckerind.*, 1938, **88**, 247.
[2] British Pharmacopœia, 1932, p. 596.
[3] *Ind. Eng. Chem. (Anal.)*, 1939, **11**, 80.
[4] H. H. Willard and G. H. Ayres, *ibid.*, 1940, **12**, 287.
[5] Cf. *Ann. Reports*, 1938, **35**, 394.
[6] R. H. Müller, *Ind. Eng. Chem. (Anal.)*, 1939, **11**, 1.

errors involved and the sensitivity of photometric methods have been discussed.[7]

From the point of view of colorimetry, organic compounds may be divided into two classes. One of these consists of substances which can be determined directly in virtue of their own colour; the other comprises substances which afford a suitable colour only when treated with a reagent. If the substance to be determined is the only coloured substance in the medium, or if any absorption due to other substances can be made ineffective by the use of suitable colour filters, the concentration of the substance in question can be determined in terms of the fraction of incident light absorbed. For example, as little as $0 \cdot 1$ μg. of chlorophyll in acetone can be determined by observations with a vacuum thermocouple in the region of the red absorption band and carotenoid pigments do not interfere,[8] or a photoelectric colorimeter with suitable filters may be used.[9]

Although the compound to be determined is sufficiently coloured, it may be associated with other coloured compounds which must be removed, otherwise they would contribute to the magnitude of the colorimetric observations. This applies to the determination in foodstuffs of carotene, which is of considerable importance as the precursor of vitamin-A. The pigments, after extraction by means of solvents and saponification, are separated by partition processes employing various solvents.[10] The resulting " carotene " solutions appear, in several cases, to contain a considerable proportion of colouring matter which is not carotene. The yellow pigment extracted from flour is an example of this.[11] In the case of extracts of leaf material, the xanthophyll may be removed from the carotene by shaking the petroleum solution with specially prepared magnesium hydroxide.[12] Some foodstuffs, e.g., tomatoes, contain lycopene or other red pigments which are not completely removed by the xanthophyll adsorbent, but a specially prepared magnesium carbonate was found to adsorb both xanthophyll and lycopene but not carotene.[13] The percentages of the different coloured components of paprika vary, and since the total colour

[7] S. E. Q. Ashley, Ind. Eng. Chem. (Anal.), 1939, 11, 72.

[8] E. S. Johnston and R. L. Weintraub, Smithsonian Misc. Coll., 1939, 98, 1.

[9] H. G. Petering, W. Wolman, and R. P. Hibbart, Ind. Eng. Chem. (Anal.), 1940, 12, 148.

[10] W. M. Seaber, Analyst, 1940, 65, 266.

[11] V. E. Munsey, J. Assoc. Off. Agric. Chem., 1938, 21, 331.

[12] G. S. Fraps and A. R. Kemmerer, ibid., 1939, 22, 190.

[13] G. S. Fraps, A. R. Kemmerer, and S. M. Greenberg, ibid., 1940, 23, 422, 659.

does not adequately evaluate the article, these pigments are separated chromatographically and determined colorimetrically.[14]

A means of eliminating the effect of interfering coloured substances is illustrated in the determination of riboflavin (or lactoflavin, a constituent of the vitamin-B_2 complex) in yeast and yeast products. Coloured substances in the filtered hydrochloric acid hydrolysate are reduced with sodium dithionite (hyposulphite or hydrosulphite) at p_H 3·5—4, the reduced riboflavin is reoxidised by shaking with air, and the light transmission is measured photo-electrically. Then the vitamin is 90% reduced with sodium dithionite and the residual colour is determined. The difference between the two readings is a measure of the riboflavin.[15] In the case of riboflavin extracts from other materials, some interfering substances are removed by preliminary oxidation with potassium permanganate before the light absorption measurements are made.[16]

In the majority of cases, the substance to be determined is colourless or insufficiently coloured for that property to be used directly as a means of determination at the dilution in question. Therefore, a reagent is sought which gives a sufficiently intense and stable colour. As an example, as little as 0·5 mg. of nitro-ethane in 25 ml. of aqueous solution, when treated with sodium hydroxide, acidified, and then immediately treated with ferric chloride, affords a red colour which is compared with similarly prepared standards. Nitropropane and nitrobutane can be determined similarly, but the colour fades too rapidly in the case of the *iso*propane and *iso*butane compounds, and nitromethane does not give a colour.[17] Small quantities of 2-methyl-1 : 4-naphthaquinone, which has some of the characters of vitamin-K—the blood-coagulation vitamin—are determined by means of the yellow colour produced when the alcoholic solution is treated with alcoholic ammonia and ethyl cyanoacetate, followed by potassium hydroxide.[18]

It is recognised that many colour reactions depend upon the presence of certain groupings in the molecule of the compound to be determined. Diazotised p-aminoacetophenone is said to be a specific reagent for the thiazole grouping in aneurin (vitamin-B_1, thiamin), giving a purple-red substance [19] which is soluble in certain organic solvents, thereby affording a colorimetric determination

[14] L. Cholnoky, *Z. Unters. Lebensm.*, 1939, **78**, 157.

[15] A. E. Schumacher and G. F. Heuser, *Ind. Eng. Chem. (Anal.)*, 1940, **12**, 203.

[16] G. Lunde, H. Kringstad, and A. Olsen, *Z. physiol. Chem.*, 1939, **260**, 141.

[17] E. W. Scott and J. F. Treon, *Ind. Eng. Chem. (Anal.)*, 1940, **12**, 189.

[18] J. L. Pinder and J. H. Singer, *Analyst*, 1940, **65**, 7.

[19] H. J. Prelubda and E. V. McCollum, *J. Biol. Chem.*, 1939, **127**, 495.

of the vitamin-B_1 content of various natural products,[20] but aneurin phosphates escape determination unless hydrolysed.[21]

The recognition of nicotinic acid as an antipellagra vitamin has stimulated the study of its colour reactions,[22] and the yellow colour produced when the pyridine ring reacts with cyanogen bromide and an aromatic amine is also given by nicotinamide, nicotinuric acid, and nicotine, the relative colour intensities produced by equimolar concentrations being, respectively, 100 : 142 : 42 : 8 when metol is the aromatic amine. The total nicotinic acid (free and combined) in a mixture is determined as such if a preliminary hydrolysis with an alkali is carried out.[23] p-Aminoacetophenone gives a more intense colour than aniline or metol, and in order to obtain reproducible results the colour reaction is conducted at p_H 6 and the solutions are protected as far as possible from light.[24] The last method determines as little as 1 μg. of nicotinic acid per g. of material after this has been hydrolysed with alkali and certain substances precipitated by alcohol. Before hydrolysis, nicotinamide gives only 20% of the colour produced by nicotinic acid, whereas nicotindiethylamide gives a more intense colour. Pyridine, α-aminopyridine, and nipecotic acid give much less intense colours than nicotinic acid, and many amino-acids and the pyridine derivatives adermin, trigonelline, and quinolinic acid give negative results. The difficulties to be faced in adjusting the conditions in order to make a colorimetric reaction specific or even highly selective are illustrated by the observation that certain cereals appear to contain more nicotinic acid (determined colorimetrically) than corresponds with the biological activity.[25] The above results also illustrate that the intensity of the colour produced by a particular reaction is affected by changes in the attachments to the reactive grouping of the molecule under investigation as well as by those of the reagent.

The nature of other substances present along with that to be determined may make a preliminary separation desirable, but this may not always be practicable. In such cases, the selectivity of the reagent producing the colour is particularly important. The creatine and creatinine contents of meat and other extracts and of biological fluids are diagnostically significant. After preliminary treatment, the creatinine, into which creatine is converted, is

[20] M. E. Auerbach, *J. Amer. Pharm. Assoc.*, 1940, **29**, 313.
[21] D. Melnick and H. Field, junr., *J. Biol. Chem.*, 1939, **127**, 531.
[22] W. R. Ashford and R. H. Clark, *Trans. Roy. Soc. Canada*, 1939, [iii], **33**, III, 29.
[23] E. Bandier, *Biochem. J.*, 1939, **33**, 1787.
[24] L. J. Harris and W. D. Raymond, *ibid.*, p. 2037.
[25] E. Kodicek, *ibid.*, 1940, **34**, 712, 724.

usually determined by means of the yellow colour produced with picric acid and sodium hydroxide, but 3 : 5-dinitrobenzoic acid is found to be a more selective reagent, albeit the colour produced is less stable.[26]   Micro-determination in plasma and serum may be effected by conversion into methylguanidine with yellow mercuric oxide and measurement of the red colour produced with α-naphthol and hypobromite.[27]

<p align="center">FLUORESCENCE METHODS.</p>

If a substance emits light while it is absorbing radiation, it is said to fluoresce.   Fluorescence differs from the Raman effect [28] in that the latter is due to the scattering of light by molecules, whereas fluorescence results from the absorption of radiation. Fluorescent light is generally of longer wave-length than that of the incident radiation, and when spectrally resolved is usually found to consist of bands, the nature and wave-lengths of which are characteristic of the substance concerned.   For example, the characteristic fluorescence bands shown by europium, ytterbium, samarium, and thulium can be used for the detection of small amounts of these elements,[29] and fluorescence spectrum measurements allow the detection of 0·01, 0·1, and 100 p.p.m. of terbium, cerium, and europium, respectively, in solution.[30]   m-Diamines are detected by the bright yellowish-green fluorescence of the diaminoacridines formed by heating with zinc chloride, glycerol, and oxalic acid.   A phenolic group interferes with the test, but if the zinc chloride is half replaced with stannous chloride, m-orientation in aminonitro- or dinitro-compounds can be detected by the fluorescent diaminoacridines produced.[31]   The fluorescence of the porphyrins has been investigated extensively, and the determination of the concentration of these substances by the fluorescence spectra of their solutions is described.[32]   Increased excretion of porphyrin is associated with lead poisoning, and the characteristic red fluorescence appears to be the most sensitive and accurate method of determining coproporphyrin-III.[33]

Fluorescence is, however, often markedly influenced by numerous

[26] E. Komm and H. Pinder, Z. Unters. Lebensm., 1939, **78**, 113.

[27] A. Riegert, Compt. rend. Soc. Biol., 1939, **132**, 535.

[28] Ann. Reports, 1938, **35**, 394.

[29] K. Przibram, Mikrochim. Acta, 1938, **3**, 68.

[30] A. Zaidel, J. Larionov, and A. N. Filippov, J. Gen. Chem. Russia, 1938, **8**, 943.

[31] A. Albert, J., 1939, 920.

[32] A. Keys and J. Brugsch, J. Amer. Chem. Soc., 1938, **60**, 2135.

[33] M. Meyer, Süddeut. Apoth.-Ztg., 1939, **78**, 138.

factors operating during observation, and it is the recognition and control of these that must precede the acceptance of a fluorescence procedure as a trustworthy analytical method. Some of these points will be illustrated in the sequel.

Light Sources.—Ultra-violet radiation of wave-length between 3000 A. and 4000 A. is generally employed for exciting the fluorescence, which is usually of low intensity relative to the source. Consequently, the exciting radiation must be of high intensity and, for quantitative work, should be constant for long periods. In addition to modern types of mercury arc, an iron vacuum arc and an iron arc cored with iron–carbon mixture satisfy the conditions.[34] Visible light is removed from the exciting radiation by means of a light filter, such as Wood's glass.

Instruments.—There is a fairly close parallel between the types of instrument used in fluorescence studies and in colorimetry. The colour and intensity of the fluorescence may be matched subjectively in terms of trichromatic coefficients, *e.g.*, in the Donaldson colorimeter.[35] The fluorescence may be compared visually or photoelectrically with standards in a photometer or may be observed spectrometrically and recorded spectrographically. The last process may involve exposing a sensitive photographic plate for many hours, but in cases where the spectrum is specific for a substance, it is of value in identification and it also facilitates the selection of colour filters and standards having the appropriate spectral characteristics.

Methods.—It is not unusual for solutions of fluorescing organic substances to undergo changes—photochemical, oxidative, etc.— which alter the characteristics of the fluorescence and make such solutions unsatisfactory as standards, particularly in routine work. For instance in the determination of aneurin (vitamin-B_1) by oxidation to thiochrome, which is determined fluorometrically, quinine sulphate lacks stability as a standard but a piece of fluorspar has been found suitable.[36] The riboflavin content of milk is rapidly determined with a mean error of $\pm 2\%$ by comparing photoelectrically the fluorescence of the filtered acetone–milk mixture with that of a piece of uranium glass which is calibrated against solutions of pure riboflavin under the same conditions. The fluorescence is so intense that amplification of the photocell current is unnecessary, but fluorescein and riboflavin are not used as standards in routine work owing to photodecomposition. However, this decomposition is not so rapid as to introduce a significant error if, as in the deter-

[34] C. E. White, *Ind. Eng. Chem. (Anal.)*, 1939, **11**, 63.

[35] R. Donaldson, *Proc. Physical Soc.*, 1935, **47**, 1068.

[36] R. G. Booth, *J. Soc. Chem. Ind.*, 1940, **59**, 181.

mination of the vitamin in the sample, a single observation lasting only 3 seconds is sufficient.[37]

The fluorometric determination of an ingredient of a mixture does not always depend on its own fluorescence or that of the main product of a reaction. For example, the determination of 0·05—1·0% of o-nitrophenol in p-nitrophenol depends on the observation that o-aminophenol (e.g., produced by reduction of o-nitrophenol) reacts with benzoic acid to form phenylbenzoxazole and associated fluorescent by-products, whereas m- and p-aminophenols do not. The fluorescence of the washed benzene extract is compared with that obtained similarly from mixtures of known composition.[38]

Fluorescence methods are also valuable in inorganic analysis, as, e.g., in the detection and determination of small quantities of aluminium. The first direct test to differentiate this metal from beryllium depends upon as little as $0·2$ μg. of the former producing an orange-red fluorescence with Pantochrome Blue Black R (the zinc salt of 4-sulpho-2 : 2'-dihydroxyazonaphthalene) in presence of acetic acid, but certain elements interfere.[39] It has not been possible to adapt this reaction for quantitative work, but morin, the dyeing principle of fustic wood, gives an intense green fluorescence with aluminium, and by adding enough reagent to give maximum fluorescence and at the same time keeping the concentration of alcohol constant, as little as $0·0005$ μg. of aluminium at a concentration of $0·1—1·2$ mg./l. can be determined fluorometrically.[40] However, various ions interfere, and beryllium, gallium, indium and the rare earths give a fluorescence similar to that of aluminium.

There are numerous examples of fluorescent substances being used as indicators. Aluminium may be determined by titrating alkali fluorides in presence of sodium chloride with an alcoholic solution of aluminium chloride containing morin, the end point being characterised by fluorescence occurring when $Al^{···}$ ceases to be removed as the non-fluorescent AlF_6'''.[41] The end-points of the iodine–sodium thiosulphate and the arsenious oxide–bromate titrations in the presence of coloured ions are indicated by α-naphthaflavone, of which the ultra-violet-excited blue fluorescence appears after removal of free iodine or bromine.[42]

Limitations of space permit reference to only a small proportion of recent work, but a full account of the diverse applications of

[37] D. B. Hand, *Ind. Eng. Chem. (Anal.)*, 1939, **11**, 306.
[38] W. Seaman, A. R. Norton, and O. E. Sundberg, *ibid.*, 1940, **12**, 403.
[39] C. E. White and C. S. Lowe, *ibid.*, 1937, **9**, 430.
[40] *Idem, ibid.*, 1940, **12**, 229.
[41] A. Okac, *Coll. Czech. Chem. Comm.*, 1938, **10**, 177.
[42] H. Gotô, *Sci. Rep. Tôhoku*, 1940, **29**, 1.

fluorescence analysis as late as 1939 has been published by J. A. Radley and J. Grant.[43]

<div align="center">ELECTROLYTIC ANALYSIS.</div>

Electrodeposition has previously received only occasional and brief mention, and a survey of recent advances in this field of analysis, in which standard methods[1] already exist for the determination in certain circumstances of a large number of metals, is deserved. That the material to be determined is usually obtained in elemental form and weighed as such, instead of as some compound to the weight of which a conversion factor has to be applied, appeals to the analyst : but the appeal may be mainly æsthetic, and the justification of higher accuracy should be proved for each method and not presumed.

General Considerations.—The potential difference, π, between a metal and a solution of its own ions is given by the Nernst equation

$$\pi = \frac{0 \cdot 0002T}{v} \log \frac{[\text{ion}]}{k}, \text{ or } \pi = \pi_0 + \frac{0 \cdot 0002T}{v} \log [\text{ion}]$$

where v is the valency of the ion, π_0 is the standard potential when the ions are at concentration of 1 g-ion/l., and the other symbols have their usual significance. At 17° this equation becomes

$$\pi = \pi_0 + (0 \cdot 058/v) \log [\text{ion}] \quad . \quad . \quad . \quad . \quad (1)$$

The standard potential, as defined above, of the hydrogen electrode is taken as zero on the hydrogen scale of potential, to which the potential of any other electrode is usually referred. If the hydrogen electrode is combined with some other electrode, and the e.m.f. of the resulting cell measured, this e.m.f. is equal to the single potential of the other electrode, and the sign of this potential is positive or negative according as the other electrode is the positive or negative pole of the cell, e.g., Na, − 2·7 v.; Fe, − 0·44 v.; Ni, − 0·23 v.; Sb, 0·1 v.; Cu, 0·34 v.; Ag, 0·8 v. From equation (1) it will be seen that the lower the concentration of a metal ion in solution, the less positive (or more negative) is the potential of the metal electrode, e.g., the cathode of an electrolytic cell, in contact with it. To deposit a metal, the potential of the cathode must be slightly more negative than the equilibrium value, and since π changes by $0 \cdot 058/v$ volts for a ten-fold change in concentration, to effect a reduction to one ten-thousandth (*i.e.*, 1 g. to 0·0001 g.)

[43] " Fluorescence Analysis in Ultra-Violet Light," 3rd Edition, Chapman & Hall, 1939.

[1] H. J. S. Sand, "Electrochemistry and Electrochemical Analysis," Vols. I and II, Blackie & Son, Ltd., 1940.

for a bivalent ion, the cathode potential has to change by $- (0.058/2) \times 4 = - 0.116$ v., and double this value for a univalent ion. Hence, provided the standard potentials of two metals differ by more than 0.2 volt, practically complete electrolytic separation should be possible, the metal with the more positive potential being deposited first. H. J. S. Sand,[2] realising the fundamental importance of the cathode potential in electrolytic depositions and separations, initiated for its measurement and control the use of an auxiliary electrode (usually a saturated potassium chloride calomel electrode) in the system. The construction of a suitable electrode vessel has been described,[3] and recent developments based upon its use are reported later.

According to the simple theory outlined above, in the electrolysis of a N-acid solution, hydrogen should be evolved at a potential of 0 v., and with a N-alkali solution at a potential of $- 0.8$ v. In fact, a potential in excess of that calculated, *i.e.*, an overpotential, usually has to be applied before hydrogen is evolved, and the value of the overpotential varies with the nature of the metal and its physical state. The existence of this phenomenon makes the deposition of certain metals with a more negative potential than that of hydrogen practicable. Overvoltages are most marked in the case of gases, and it is to reduce the anodic overvoltage, or anodic polarisation, of oxygen that reducing agents are frequently added to solutions for electrolysis. Lindsey and Sand [4] have investigated the efficiency of the sulphates and hydrochlorides of hydrazine and hydroxylamine as anodic depolarisers under varying conditions of temperature and current density, and conclude that hydrazine salts appear to be efficient under all conditions, whilst the efficiency of hydroxylamine, though smaller, is improved by the presence of chlorine and copper ions. The overpotential during the deposition of most metals is usually very small ($\ll 0.1$ v.), and hence the deposition of metals at the cathode is an almost truly reversible process to which the Nernst equation can be applied. Iron, cobalt, and nickel, with overvoltages of about 0.25 v., were observed by S. Glasstone [5] to be exceptional, though at $90°$ they behaved practically normally.

The deposition of a metal from a solution of its complex ions frequently requires a more negative cathode potential than from a simple salt solution, since the effective concentration of simple metal ions is reduced by complex formation. This change in deposition potential, similar in its effect to an overvoltage, is in

[2] *J.*, 1907, **91**, 373.
[3] A. J. Lindsey and H. J. S. Sand, *Analyst*, 1934, **59**, 329.
[4] *Idem, ibid.*, 1935, **60**, 739.   [5] *J.*, 1926, 2887.

fact a concentration polarisation, and Glasstone [6] so ascribes the higher cathode potentials necessary for the deposition of the metals from argenti- and cupro-cyanide solutions. Its effect is clearly of analytical use, since the shift in the deposition potentials may in certain cases permit the electrolytic separation of two metals which when they are present wholly as their simple ions is not practicable.

Since it is the concentration of the ions in the immediate vicinity of the cathode that determines the potential difference, π, the desirability of stirring the electrolyte becomes evident. At low current densities, the ions migrate and diffuse into the cathode layer at a rate equal to that of deposition, but on increasing the current density a limiting value is reached beyond which the cathode potential rises until the deposition of other ions occurs. This limiting value of the current density is raised considerably by stirring and by increasing the temperature, and both devices are commonly employed to facilitate speedy deposition. The mixing of the products of the anodic and cathodic reactions by vigorous stirring may, however, in certain cases be undesirable. High temperatures, though decreasing the resistance, increasing diffusion, and often assisting in the formation of a good adherent deposit, reduce the overvoltage of hydrogen and may cause oxidation of the deposit. O. K. Kudra [7] has examined the influence of temperature on cathode processes with particular reference to the formation of black deposits of copper and cadmium. The decrease of the hydrogen overvoltage and the consequent evolution of hydrogen is generally unwanted : it often causes spongy and non-adherent deposits, possibly due to the formation and subsequent decomposition of hydrides. When mercury or Wood's metal cathodes are used,[8] however, the liberation of hydrogen provides a simple means of agitating the solution.

General Determinations.—The influence of iron salts on the deposition of *copper* has been investigated by J. G. Fife and S. Torrance.[9] During electrolysis, oxidation of ferrous to ferric ions occurs at the anode, and since ferric ions cause redissolution of the electrolytically deposited copper, they must be reduced at the cathode before deposition of copper can take place. Small quantities of iron can be kept reduced by the addition of hydrazine or hydroxylamine salts, but when large amounts are present this treatment is inadequate. The difficulty may be overcome by

[6] *J.*, 1929, 690.
[7] *Mem. Inst. Chem. Ukrain. Acad. Sci.*, 1938, **5**, 239.
[8] H. Paweck, *Z. anal. Chem.*, 1927, **72**, 225; 1929, **79**, 115.
[9] *Analyst*, 1937, **62**, 30.

separating the revolving anode, which is immersed in an indifferent electrolyte, by a parchment diaphragm from the cathode and the solution to be analysed, the potential of the cathode being controlled throughout the analysis. Alternatively, the internal electrolytic method referred to below may be employed. M. Geloso and P. Deschamps [10] investigated the iron–copper system and observed that the critical iron concentration is lowered by increase in temperature and in the rate of agitation of the solution. M. Geloso [11] reports that re-dissolution of the copper can be prevented by the addition of a fluoride, which effectively removes the iron from the alternating oxidation–reduction processes by the formation of the complex ion $(FeF_6)'''$. The completion of the deposition of copper from dilute nitric acid solution is obtained, according to J. A. Scherrer, R. K. Bell, and W. D. Mogerman,[12] if a trace of chloride is added either during the dissolution of the alloy or before electrolysis. The influence of glycerol, acetone, methyl and ethyl alcohols on the cathode efficiency of copper deposition from acidified copper sulphate solution has been quantitatively investigated,[13] and the increase in efficiency with increasing concentration of non-electrolyte up to a limiting value is attributed to the reduced ability of the solution to redissolve deposited copper, whilst the possibility of a complex cation of bivalent copper and the non-electrolyte is recognised.

In an examination of the influence of acetone and methyl and ethyl alcohols over a wide range of concentrations on the deposition of *silver*,[14] pronounced discontinuities in the interrelationship of the concentration of non-electrolyte and cathode efficiency are thought to indicate the formation of complexes. R. Taft and L. H. Horsley [15] have made an extensive examination of the effect of the addition of 140 organic compounds and 30 inorganic salts on the deposition of silver from silver nitrate solution under standard conditions. Colloids of molecular weight greater than 250 were found to produce abnormal or striated deposits, whilst certain higher aliphatic and cyclic acids and inorganic salts gave fine crystalline deposits. The mechanism of the deposition of silver from silver nitrate solution has been elucidated by microscopic examination, and the deduction made that the number of silver nuclei forming was inversely proportional to the concentration

[10] *Bull. Soc. chim.*, 1939, [v], **6,** 1100.

[11] *Ibid.*, p. 1238.

[12] *J. Res. Nat. Bur. Stand.*, 1939, **22,** 697.

[13] S. S. Joshi, D. H. Solanki, and T. V. S. Rao, *J. Indian Chem. Soc.*, 1938, **15,** 167.

[14] S. S. Joshi and S. Padmanabhan, *ibid.*, p. 176.

[15] *Trans. Electrochem. Soc.*, 1938, **74,** 77.

of silver nitrate between 0·1 and 2N.[16] Details for an improved procedure for the deposition of silver from potassium cyanide solution have been given.[17]

Electrolytic methods have frequently been employed in micro-analysis, and a recent example is the observation that 0·4—30 μg. of *gold* may be electrolysed quantitatively by using gold-free lead cathodes,[18] the lead being subsequently eliminated by the usual methods, and the gold bead measured micrometrically. The electrolytic microdetection of traces of *copper* on shears which had been used for cutting copper wire has been described by G. W. Baker.[19] A good positive result was obtained with only 0·0002 mg. of copper per sq. mm. The precision of the microelectrolytic determination of copper has been examined.[20]

The separation of *lead* from *bismuth* was effected in earlier methods [2, 21] by first depositing the bismuth at a controlled potential, reducing agent being added, and the lead being subsequently deposited as metal. This method was recognised by E. M. Collin [22] to have certain disadvantages owing to the great tendency of the lead to oxidise on drying, and to the deleterious effect on the platinum cathode, and a modified method was devised in which, as the reducing agent during the deposition of bismuth at 80—85°, hydrazine hydrate was used, this material being advantageous in that it was subsequently easily destroyed by sodium peroxide, thus enabling the lead to be deposited as dioxide. Collin deduced an empirical conversion factor for the lead dioxide deposit to lead, and concluded that its value was dependent on the conditions of deposition and drying. The determination of lead as the electrolytically deposited dioxide has recently been the subject of investigation by W. T. Schrenk and his co-workers,[23] who found that for small quantities the composition of the anodic deposit was $9PbO_2,PbO,H_2O$, *i.e.*, substantially pure PbO_2.

The electrolytic deposition of *antimony* [24] from dilute sulphuric acid solution has been shown to be rapid and accurate (average error of $-0·1\%$ of the amount determined), even though basic

[16] A. T. Wahramian and S. A. Alemian, *Acta Physicochim. U.R.S.S.*, 1937, **7**, 95.

[17] D. Tschavdarov, *Z. anal. Chem.*, 1938, **112**, 258.

[18] M. G. Raeder and O. S. Kyllinstad, *Mikrochem.*, 1939, **27**, 112.

[19] *Analyst*, 1936, **61**, 603.

[20] W. M. MacNiven and R. A. Bournique, *Ind. Eng. Chem. (Anal.)*, 1940, **12**, 431.

[21] A. Lassieur, " Electroanalyse Rapide," Paris, 1927, p. 108.

[22] *Analyst*, 1929, **54**, 654.

[23] P. H. Delano and W. T. Schrenk; T. G. Day and W. T. Schrenk, *School Mines Met. Univ. Missouri Bull.*, 1935, Tech. Ser. No. 2, 7, 31.

[24] S. L. Jovanovitch, *Z. anal. Chem.*, 1938, **114**, 415.

antimony sulphate is precipitated in the solution.   The method may be applied to the analysis of antimony ores.

The frequently encountered difficulty of removing the residual quantities, which may amount to several mg., of *tin* in the electrolytic deposition of the metal from chloride solution has variously been attributed to the formation of the gaseous hydride, stannane, at the anode, to the volatilisation of stannic chloride during the preparation of the solution, to the redissolution of some of the deposits during washing, and to mechanical loss due to the poor quality of the deposit.   F. G. Kny-Jones, A. J. Lindsey, and A. C. Penney [25] have examined this problem, and from earlier work [26, 27] they deduced that loss of tin as stannane does not occur, whilst their own experiments show that the addition of ammonium chloride to prevent the volatilisation of stannic chloride is disadvantageous, as it promotes redissolution of the deposit.   The coating of the platinum cathode with copper diminished dissolution of the tin on washing, and the use of a low current density ensured a good adherent deposit.   The controlled cathode potential technique was used; hydroxylamine was added to prevent the anodic evolution of chlorine.

Arsenic may be determined by the electrolytic Reinsch test, but direct deposition of the metal is not easy, since the concentration of arsenic ions in solutions of its compounds is low, and any liberation of hydrogen results in the formation of arsine. S. Torrance [28] has examined this problem and has found that the quantitative deposition requires the presence of chloride ions, the simultaneous deposition of copper, and that the arsenic should be in the arsenious form.   In practice, these conditions were satisfied by preliminary reduction of the hydrochloric acid solution by sulphurous acid, the addition of copper (about five times the amount of arsenic present), and electrolysis, an auxiliary electrode being used to enable the cathode potential to be controlled.   Copper arsenide was deposited quantitatively.

The deposition of *bismuth* from chloride solutions has long presented difficulties, in that spongy deposits were liable to be formed, accompanied by a sharp rise in the auxiliary potential at an early stage of the electrolysis, possibly due to the formation at the cathode of bismuth oxychloride.   F. G. Kny-Jones [29] has found that the addition of oxalic acid prevents the formation of basic salts, and

[25] *Analyst*, 1940, **65**, 498.

[26] F. Paneth and E. Rabinovitch, *Ber.*, 1924, **57, B**, 1877.

[27] A. Schleicher and L. Toussaint, " Electroanalytische Schnellmethoden." Stuttgart, 1926, p. 191.

[28] *Analyst*, 1938, **63**, 104.   [29] *Ibid.*, 1939, **64**, 172.

electrolysis at 80—85°, using either a saturated calomel electrode or D. J. Brown's auxiliary electrode [30] (*i.e.*, a platinum wire on which a small amount of bismuth is first deposited) to control the cathode potential, gave satisfactory results. The method may be applied to the determination of bismuth in the presence of lead and tin, and hence to the analysis of ternary alloys of these three metals. The same worker has also found [31] that good deposition may be made from sulphuric and nitric acid solutions by conducting the electrolysis at a high temperature from strongly acid solution, the controlled potential technique being used with hydrazine sulphate as depolariser.

The determination of *cobalt* in ores has been described.[32] The cobalt is deposited with the nickel (since their deposition potentials are very close), and subsequent separation of the two metals is made chemically. Similarly, in the analysis of nickel bronzes, S. Torrance [33] obtained the cobalt codeposited with the nickel. Recently, however, Torrance [34] has developed a method for separating cobalt from nickel by deposition as cobaltic oxide at 90—95° on the anode, using a diaphragm electrode, as previously described, to separate the cathode from the cobalt solution. In the earlier method of A. Coehn and D. Gläser,[35] deposition of cobalt on the cathode was prevented by the addition of potassium dichromate as a depolariser, and careful adjustment of the electrical conditions, but the deposition of cobaltic oxide was slow.

The ability of any technique to play a substantial part in the analysis of a complex material is a fair indication of its value, and convincing evidence of the utility of electrolytic methods is to be found in their application to the analysis of white metals,[36] brass,[36] nickel bronzes,[33] and aluminium alloys.[33]

Electrolytic Marsh Tests.—The electrolytic reduction of *arsenic* and the subsequent decomposition by heat of the arsine has formed the basis of a number of methods for the determination of this element, and that of F. S. Aumonier,[37] in which a mercury cathode is used, has long been accepted as a standard procedure. A rapid continuous method has recently been described by H. C. Lockwood.[38] The arsenical solution flows slowly over a cadmium cathode, and details of drying the gas and the deposition of arsenic are given. The cathodic reduction of arsenic has also been

[30] *J. Amer. Chem. Soc.*, 1926, **48**, 582.

[31] *Analyst*, 1939, **64**, 575.

[32] M. M. Fine, *U.S. Bur Mines*, 1938, Rept. Invest. 3370, 59.

[33] *Analyst*, 1938, **63**, 488.   [34] *Ibid.*, 1939, **64**, 109.

[35] *Z. anorg. Chem.*, 1903, **33**, 9.

[36] S. Torrance, *Analyst*, 1937, **62**, 719.

[37] *J. Soc. Chem. Ind.*, 1927, **46**, 341.   [38] *Analyst*, 1939, **64**, 657.

investigated by L. Cambi and G. G. Monselise,[39] who report that in zinc sulphate solution reduction is inhibited if pyridine is present together with magnesium or aluminium salts (separately they have negligible effect) owing to the formation of a cathode film of pyridine and basic salts.

It is known that *germanium* is more readily reduced to mono-germane in alkaline than in acid solution, but it was not until 1934 that the electrolytic reduction in alkaline solution was attempted. As arsenates are not easily reduced in this medium, S. A. Croase's method [40] (which is based on J. Grant's determination of antimony as stibine [41]) enables germanium to be determined in the presence of large amounts of arsenic. It was found that nickel was the most satisfactory cathode metal of a number (nickel, cobalt, stainless steel, lead, magnesium, iron, and copper) examined. Optimum values of current density and alkali concentration were determined.

Internal Electrolysis.—Though C. Ullgren [42] in 1868 plated small quantities of copper from sulphate solutions which formed the electrolytes of Zn–Pt, Cd–Pt, and Al–Pt cells, no further development of this attractive method, which requires no external source of current, was made for over 60 years. H. J. S. Sand [43] and his co-workers evolved and used a technique suited to the rapid determination of small quantities of metals. A platinum-gauze cylinder as the cathode, and a pair of anodes of baser metal (*e.g.*, zinc or lead), enclosed in parchment bags and straddling the cathode and externally connected to it, make a typical set up. The solution to be analysed is the catholyte, and its composition is so adjusted, *e.g.*, by the addition of reducing agents, that redissolution of the deposited metal due to aerial oxidation is prevented. The anolyte is a solution of a salt of the anode metal of a higher concentration than that in the catholyte so that deposition of the anode metal may not occur.

The method has been found useful in a number of cases. E. A. Collin [44] has determined bismuth and copper in lead bullion, bismuth in lead ores, and cadmium and copper in sulphate solutions of spelter and zinc ores. J. G. Fife [45] preferred the use of ammine chlorides to sulphates for the separation of small amounts of cadmium from zinc, and the same author has determined nickel in zinc,[46] silver in galena and in pyrites,[47] mercury (0·7—7 mg.) in brass,[48] and

[39] *Rend. Ist. Lomb. Sci. Lett.*, 1936, [ii], **69**, 392; *Chem. Zentr.*, 1936, II, 3643.

[40] *Analyst*, 1934, **59**, 462, 747. [41] *Ibid.*, 1928, **53**, 626.

[42] *Z. anal. Chem.*, 1868, **7**, 442. [43] *Analyst*, 1930, **55**, 309.

[44] *Ibid.*, pp. 312, 495, 680. [45] *Ibid.*, 1936, **61**, 681.

[46] *Ibid.*, p. 683. [47] *Ibid.*, 1937, **62**, 723.

[48] *Ibid.*, 1938, **63**, 650.

copper in the presence of large quantities of cadmium [53] by the internal electrolytic technique. Reference has already been made to the difficulties in the electrolytic determination of small amounts of copper in the presence of large amounts of iron : the separation may be satisfactorily made by internal electrolysis.[49]

J. L. Lurie and his co-workers [49] have found that internal electrolytic processes may be conducted without the use of a diaphragm or stirrer. They emphasise the risk of deposition of the metal on the anode (i.e., " cementation "), resulting in a fall of the current and subsequent cessation of deposition on the cathode. Cementation on the anode is favoured by a large potential difference : when a nickel anode was used for the deposition of copper, cementation occurred, but deposition on the cathode was complete when a lead anode was employed. Technical modifications [50] and procedures for the determination of copper in ores,[51] cadmium and copper in zinc alloys,[52] and tin in aluminium alloys [52] have also been described.

<div align="right">

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G. W. G. MACLENNAN.
H. K. WHALLEY.

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[49] J. L. Lurie and L. B. Ginsberg, *Ind. Eng. Chem. (Anal.)*, 1937, **9**, 424; J. L. Lurie and M. I. Troitzkaia, *Ann. Chim. anal.*, 1938, **20**, 61; *Zavod. Lab.*, 1937, **6**, 33.

[50] B. L. Clarke, L. A. Wooten, C. L. Luke, *Ind. Eng. Chem. (Anal.)*, 1936, **8**, 411.

[51] N. N. Eberg, *Zavod. Lab.*, 1938, **7**, 239.

[52] B. L. Clarke and L. A. Wooten, *Trans. Electrochem. Soc.*, 1939, **76**, 339.

[53] *Analyst*, 1940, **65**, 562.

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TABLE OF ABBREVIATIONS EMPLOYED IN THE REFERENCES.

Abbreviated Title.	FULL TITLE.
A.	British Chemical and Physiological Abstracts (Section A).
Acta brev. neer. Physiol. .	Acta Brevia Neerlandica de Physiologia, Pharmacologia, Microbiologia, e.a.
Acta path. microbiol. Scand.	Acta pathologica et microbiologica Scandinavica.
Acta Physicochim. U.R.S.S.	Acta Physicochimica U.R.S.S.
Acta tuberc. Scand. . .	Acta tuberculosea Scandinavica.
Amer. Chem. J. . .	American Chemical Journal.
Agric. Col. Sweden Ann. .	Lantbruks-Högskolans Annaler, Agricultural College of Sweden.
Amer. J. Bot. . . .	American Journal of Botany.
Amer. J. Physiol. . .	American Journal of Physiology.
Amer. J. Sci. . . .	American Journal of Science.
Amer. Math. Soc. Coll. Pub.	American Mathematical Society, Collective Publications.
Analyst	The Analyst
Anat. Rec. . . .	Anatomical Record.
Angew. Chem. . .	Angewandte Chemie (formerly Zeitschrift für angewandte Chemie).
Annalen	Justus Liebig's Annalen der Chemie.
Ann. Bot. ´ . . .	Annals of Botany.
Ann. Chim. anal. . .	Annales de Chimie analytique et de Chimie appliquée.
Ann. Falsif. . . .	Annales des Falsifications.
Ann. Inst. Pasteur .	Annales de l'Institut Pasteur.
Ann. Physik . .	Annalen der Physik.
Ann. Physique . .	Annales de Physique.
Ann. Reports . .	Annual Reports on the Progress of Chemistry.
Ann. Rev. Biochem. . .	Annual Review of Biochemistry.
Ann. Soc. sci. Bruxelles	Annales de la Société Scientifique de Bruxelles.
Arch. Intern. Med. .	Archives of Internal Medicine.
Arch. int. Pharmacodyn. .	Archives internationales de Pharmacodynamie et de Thérapie.
Arch. klin. Chir. .	Archiv für klinische Chirurgie.
Arch. Pharm. . .	Archiv der Pharmazie.
Archiv. Zool. . .	Archives de Zoologie expérimentale et générale.
Arch. Mikrobiol. .	Archiv für Mikrobiologie.
Arch. Protistenkunde .	Archiv für Protistenkunde.
Arch. Sci. biol. . .	Archivio di Scienze biologiche.
Arkiv Kemi, Min. Geol. .	Arkiv für Kemi, Mineralogi och Geologi.
Atti R. Accad. Sci. Torino .	Atti della Reale Accademia della Scienze di Torino.
Atti X Cong. intern. Chim. .	Atti del X Congresso internazionale di Chimica.
B.	British Chemical and Physiological Abstracts (Section B).
Ber.	Berichte der deutschen chemischen Gesellschaft.
Biochem. J. . . .	The Biochemical Journal.
Biochem. Z. . . .	Biochemische Zeitschrift.
Biol. Rev. . . .	Biological Reviews.
Biol. Zentr. . . .	Biologisches Zentralblatt.
Bot. Gaz.	Botanical Gazette.
Brit. Dental J. . .	British Dental Journal.
Brit. J. Exp. Path. .	British Journal of Experimental Pathology.

Abbreviated Title.	Full Title.
Brit. J. Urol. . . .	British Journal of Urology.
Brit. Med. J. . . .	The British Medical Journal.
Bull. Acad. roy. Belg.	Académie royale de Belgique—Bulletin de la Classe des Sciences.
Bull. Acad. Sci. Roumaine .	Bulletin de la Section Scientifique de l'Académie Roumaine.
Bull. Biol. Méd. exptl. U.R.S.S.	Bulletin de Biologie et Médicine experimentale de l'U.R.S.S.
Bull. Chem. Soc. Japan .	Bulletin of the Chemical Society of Japan.
Bull. Chim. Soc. Romāne .	Buletinul de Chimie pura si aplicata al Societatii Romāne de Chimie.
Bull. Soc. chim. . .	Bulletin de la Société chimique de France.
Bull. Soc. chim. Belg. .	Bulletin de la Société chimique de Belgique.
Bull. Soc. Chim. biol. .	Bulletin de la Société de Chimie biologique.
Bul. Soc. Chim. Romānia .	Buletinul Societătii de Chimie din Romānia.
Bull. Soc. sci. Bretagne .	Bulletin de la Société scientifique de Bretagne.
Bull. Torrey Bot. Club .	Bulletin of the Torrey Botanical Club.
Bur. Stand. J. Res. . .	Bureau of Standards Journal of Research (now Journal of Research of the National Bureau of Standards).
Canadian J. Res. . .	Canadian Journal of Research.
Canadian Med. Assoc. J. .	Journal of the Canadian Medical Association.
Cereal Chem. . . .	Cereal Chemistry.
Chem. and Ind. . .	Chemistry and Industry.
Chem. Reviews . . .	Chemical Reviews.
Chem. Weekblad . .	Chemisch Weekblad.
Chem. Zentr. . . .	Chemisches Zentralblatt.
Chinese J. Physiol. . .	Chinese Journal of Physiology.
Coll. Czech. Chem. Comm. .	Collection of Czechoslovak Chemical Communications.
Colloid. J., U.S.S.R. . .	Colloidal Journal, U.S.S.R.
Compt. rend. . . .	Comptes rendus hebdomadaires des Séances de l'Académie des Sciences.
Compt. rend. Acad. Sci. U.R.S.S.	Comptes rendus de l'Académie des Sciences de l'Union des Républiques Soviétiques Socialistes.
Compt. rend. Soc. Biol. .	Comptes rendus hebdomadaires de Séances de la Société de Biologie.
Contr. Boyce Thompson Inst.	Contributions from the Boyce Thompson Institute.
Ergebn. Physiol. . .	Ergebnisse der Physiologie.
Ergebn. exakt. Naturw. .	Ergebnisse der exakten Naturwissenschaften.
Ergebn. Enzymforschung .	Ergebnisse der Enzymforschung.
Finska Kem. Medd. . .	Finska Kemistamfundets Meddelanden (Suomen Kemistiseuran Tiedonantoja).
Geneesk. Tijdschr. Nederl.-Indië	Geneeskundig Tijdschrift voor Nederlandsch-Indië.
Helv. Chim. Acta . .	Helvetica Chimica Acta.
Helv. Physica Acta . .	Helvetica Physica Acta.
Ind. Eng. Chem. . .	Industrial and Engineering Chemistry.
Ind. Eng. Chem. (Anal.)	Industrial and Engineering Chemistry : Analytical Edition.
Indian J. Med. Res. . .	Indian Journal of Medical Research.
J.	Journal of the Chemical Society.
J. Agric. Res. . .	Journal of Agricultural Research.
J. Agric. Sci. . .	Journal of Agricultural Science.
J. Amer. Chem. Soc. . .	Journal of the American Chemical Society.
J. Amer. Med. Assoc. .	Journal of the American Medical Association.
J. Amer. Pharm. Assoc. .	Journal of the American Pharmaceutical Association.
J. Appl. Physics . .	Journal of Applied Physics.
J. Assoc. Off. Agric. Chem. .	Journal of the Association of Official Agricultural Chemists.
J. Bact.	Journal of Bacteriology.
J. Biochem. Japan . .	Journal of Biochemistry, Japan.
J. Biol. Chem. . . .	Journal of Biological Chemistry.

Abbreviated Title.	FULL TITLE.
J. Cell. Comp. Physiol.	Journal of Cellular and Comparative Physiology.
J. Chem. Physics	The Journal of Chemical Physics.
J. Chim. physique	Journal de Chimie physique.
J. Clin. Invest.	Journal of Clinical Investigation, The.
J. Egypt. Med. Assoc.	Journal of the Egyptian Medical Association.
J. Endocrinol.	Journal of Endocrinology.
J. Exp. Med.	Journal of Experimental Medicine.
J. Exp. Zoology	Journal of Experimental Zoology.
J. Fish. Res. Bd. Can.	Journal of the Fisheries Research Board, Canada.
J. Gen. Chem. Russia	Journal of General Chemistry (U.S.S.R.) (formerly chemical part of the Journal of the Physical and Chemical Society of Russia).
J. Gen. Physiol.	Journal of General Physiology.
J. Hyg.	Journal of Hygiene.
J. Immun.	Journal of Immunology.
J. Indian Chem. Soc.	Quarterly Journal of the Indian Chemical Society.
J. Inst. Brew.	Journal of the Institute of Brewing.
J. Inst. Elect. Eng.	Journal of the Institution of Electrical Engineers.
J. Inst. Petroleum	Journal of the Institute of Petroleum.
J. Lab. Clin. Med.	Journal of Laboratory and Clinical Medicine.
J. Oil Colour Chem. Assoc..	Journal of the Oil and Colour Chemists' Association.
J. Nutrition	Journal of Nutrition.
J. Opt. Soc. Amer.	Journal of the Optical Society of America.
J. Org. Chem.	The Journal of Organic Chemistry.
J. Pharm. Exp. Ther.	Journal of Pharmacology and Experimental Therapeutics.
J. Pharm. Soc. Japan	Journal of the Pharmaceutical Society of Japan (Yakugakuzasshi).
J. Phys. Chem. Russia	Journal of Physical Chemistry, Russia (Zhurnal Fizitscheskoi Chimii).
J. Physical Chem.	The Journal of Physical Chemistry.
J. Phys. Radium	Journal de Physique et le Radium.
J. Physiol.	Journal of Physiology.
J. pr. Chem.	Journal für praktische Chemie.
J. Proc. Roy. Soc. N.S.W..	Journal and Proceedings of the Royal Society of New South Wales.
J. Res. Nat. Bur. Stand.	Journal of Research of the National Bureau of Standards (formerly Bureau of Standards Journal of Research).
J. Russ. Phys. Chem. Soc..	Journal of the Russian Physical and Chemical Society.
J. Soc. Chem. Ind., Japan .	Journal of the Society of Chemical Industry, Japan.
J. Sci. Instr.	Journal of Scientific Instruments.
J. Soc. Chem. Ind.	Journal of the Society of Chemical Industry.
Jahrbuch wiss. Bot.	Jahrbuch für wissenschaftliche Botanik.
K. fysiogr. Sällsk. Lund Forh.	Kongliga Fysiografiska Sällskapets i Lund Forhandlinger.
Kgl. Danske Vid. Selskab, Math.-Fys. Medd.	Kongelige Danske Videnskabernes Selskab, Mathematisk-Fysiske Meddelelser.
Kgl. Norske Videnskab. Selskabs Skrifter	Kongelige Norske Videnskabernes Selskabs Skrifter.
Klin. Woch.	Klinische Wochenschrift.
Kolloid-Z.	Kolloid-Zeitschrift.
Kolloid-Beih.	Kolloid-Beihefte.
Lancet	The Lancet.
Mem. Acad. R. Sc. Lettres Danemark	Memoires de l'Académie des Sciences et des Lettres de Danemark.
Mem. Coll. Sci., Kyoto Imp. Univ.	Memoirs of the College of Science, Kyoto Imperial University.
Mem. Inst. Chem. Ukrain. Acad. Sci.	Memoirs of the Institute of Chemistry, Academy of Sciences of the Ukrainian S.S.R.
Mem. Manchester Lit. Phil. Soc.	Memoirs and Proceedings of the Manchester Literary and Philosophical Society.

Abbreviated Title.	FULL TITLE.
Mikrochim. Acta	Mikrochimica Acta.
Monatsh.	Monatshefte für Chemie und verwandte Teile anderer Wissenschaften.
Naturwiss.	Die Naturwissenschaften.
Nederland. Tijdschr. Natuurkunde	Nederlandsch Tijdschrift voor Natuurkunde.
New England J. Med.	New England Journal of Medicine.
Nord. med. Tidsskr.	Nordisk medicinisk Tidsskrift.
Pharm. Weekblad	Pharmaceutisch Weekblad.
Phil. Mag.	Philosophical Magazine (The London, Edinburgh and Dublin).
Phil. Trans.	Philosophical Transactions of the Royal Society.
Physical Rev.	Physical Review.
Physikal. Z.	Physikalische Zeitschrift.
Physikal. Z. Sovietunion	Physikalische Zeitschrift der Sowjetunion.
Post Grad. Med. J.	Post Graduate Medical Journal.
Poultry Sci.	Poultry Science.
Proc. Amer. Acad. Arts Sci.	Proceedings of the American Academy of Arts and Sciences.
Proc. Camb. Phil. Soc.	Proceedings of the Cambridge Philosophical Society.
Proc. Imp. Acad. Tokyo	Proceedings of the Imperial Academy (Tokyo).
Proc. Indian Acad. Sci.	Proceedings of the Indian Academy of Science.
Proc. Indiana Acad. Sci.	Proceedings of the Indiana Academy of Science.
Proc. K. Akad. Wetensch. Amsterdam.	Koninklijke Akademie van Wetenschappen te Amsterdam (Proceedings, English version).
Proc. London Math. Soc.	Proceedings of the London Mathematical Society.
Proc. Nat. Acad. Sci.	Proceedings of the National Academy of Sciences.
Proc. Physical Soc.	Proceedings of the Physical Society of London.
Proc. Roy. Irish Acad.	Proceedings of the Royal Irish Academy.
Proc. Roy. Soc.	Proceedings of the Royal Society.
Proc. Soc. Exp. Biol. Med..	Proceedings of the Society for Experimental Biology and Medicine.
Proc. XVI Intern. Physiol. Cong., Zurich	Proceedings of the XVI International Physiological Congress, Zurich.
Publ. Health Reps., Wash.	Public Health Reports, Washington.
Pubns. Amer. Assoc. Adv. Sci.	Publications of the American Association for the Advancement of Science.
Rec. Trav. chim.	Recueil des Travaux chimiques des Pays-Bas et de la Belgique.
Rend. Ist. Lomb. Sci. Lett.	Rendiconti dell' Reale Istituto Lombardo di Scienze e Lettere.
Rev. Mod. Physics	Reviews of Modern Physics.
Rev. Immunol.	Revue d'Immunologie.
Rev. Sci. Instr.	Review of Scientific Instruments.
Rocz. Chem.	Roczniki Chemji organ Polskiego Towarzystwa Chemicznego.
School Mines Met. Univ. Missouri Bull.	Bulletin of the School of Mines and Metallurgy, University of Missouri.
Schweiz. med. Woch.	Schweizerische medizinische Wochenschrift.
Sci. Papers Inst. Phys. Chem. Res. Tokyo.	Scientific Papers of the Institute of Physical and Chemical Research, Tokyo.
Sci. Rep. Tôhoku.	Science Reports, Tôhoku Imperial University.
Smithsonian Misc. Coll.	Smithsonian Miscellaneous Collection.
Soc. Sci. Fenn. Phys. Math.	Societas Scientiarum Fennica, Commentationes Physico-Mathematicae.
Süddeut. Apoth.-Ztg.	Süddeutsche Apotheker-Zeitung.
Suomen Kem.	Suomen Kemistilehte (Acta Chemica Fennica).
Svensk Kem. Tidskr.	Svensk Kemisk Tidskrift.
Svensk Vet. Akad. Arkiv Mat. Ast. Fys.	Arkiv för Matematik, Astronomi och Fysik, Kongliga Svenska Vetenskaps Akademiens Handlingar.
Trans. Electrochem. Soc.	Transactions of the Electrochemical Society.
Trans. Faraday Soc..	Transactions of the Faraday Society.

Abbreviated Title.		FULL TITLE.
Trans. Roy. Soc. Canada	.	Transactions of the Royal Society of Canada.
Veröff. Siemens-Konz.	.	Veröffentlichungen aus Siemens-Konzern (now Wissenschaftliche Veröffentlichungen aus den Siemens-Werken.
Wied. Ann. . .	.	Wiedemanns Annalen der Physik.
Wiss. Veröff. Siemens-Werken		Wissenschaftliche Veröffentlichungen aus den Siemens-Werken.
Z. anorg. Chem. .	.	Zeitschrift für anorganische und allgemeine Chemie.
Z. Elektrochem. .	.	Zeitschrift für Elektrochemie (und angewandte physikalische Chemie).
Z. Krist. . . .	.	Zeitschrift für Kristallographie.
Z. Physik . .	.	Zeitschrift für Physik.
Z. physikal. Chem. .	.	Zeitschrift für physikalische Chemie, Stöchiometrie und Verwandtschaftslehre.
Z. physiol. Chem. .	.	Hoppe-Seyler's Zeitschrift für physiologische Chemie.
Zavod. Lab. . .	.	Zavodskaja Laboratorija.
Zentr. Bakt. Par. .	.	Zentralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten.
Z. Unters. Lebensm. . .	.	Zeitschrift für Untersuchung der Lebensmittel.
Z. Wirts. Zuckerind. . .	.	Zeitschrift der Wirtschaftsgruppe Zuckerindustrie (Verein der Deutschen Zucker-Industrie).

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